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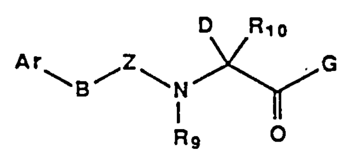

(I)

(57) Abstract

A CCK antagonist compound of formula (I) wherein G is (1) NH_2 or (2) substituted amino; R_9 is (1) hydrogen, (2) loweralkyl, (3) carboxy-substituted alkyl or (4) carboxyester-substituted alkyl; R_{10} is (1) hydrogen, (2) loweralkyl, (3) functionalized alkyl or (4) cycloalkyl; D is (1) hydrogen, (2) loweralkyl, (3) functionalized alkyl, (4) cycloalkyl, (5) aryl, (6) functionalized oxyalkyl or (7) heterocyclic; with the proviso that D is other than indolylmethyl, indolinylmethyl or oxindolylmethyl; or R_{10} taken together with D or R_9 taken together with D forms a cyclic group; Z is (1) -C(O)-, (2) -C(S)- or (3) -$S(O)_2$-; B is (1) absent, (2) alkylene, (3) alkenylene, (4) substituted alkenylene, (5) -R_{26}-R_{27}- wherein R_{26} is absent or -CH_2- and R_{27} is -O-, -S-, -NH- or -N(loweralkyl)- or (6) -R_{27}-CH_2- wherein R_{27} is defined as above; and Ar is (1) aryl or (2) a heterocyclic group.

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AMINO ACID ANALOG CCK ANTAGONISTS

This is a continuation-in-part of U.S. Patent application Serial No. 376,778, filed July 7, 1989, which is a continuation-in-part of PCT patent application Serial No. PCT/US89/01412, filed April 4, 1989, which is a continuation-in-part of U.S. patent application Serial No. 177,715, filed April 5, 1988.

Technical Field

The present invention relates to compounds and compositions which antagonize cholecystokinin and gastrin, processes for making such compounds, synthetic intermediates employed in these processes and a method for treating gastrointestinal disorders, central nervous system disorders, cancers of the gastrointestinal system (i.e., pancreas, gall bladder, etc.), hypoinsulinemia, or

potentiating analgesics, or regulating appetite disorders with such compounds.

Background of the Invention

Cholecystokinins (CCK) are a family of polypeptide hormones. CCK and a 33 amino acid fragment of CCK (CCK_{33}) were first isolated from hog intestine. (Mutt and Jorpes, Biochem. J. 125, 628, 1981). Recently the CCK_{33} fragment has been found in the brain, where it appears to be the precursor of two smaller fragments, an octapeptide CCK_8 and a tetrapeptide CCK_4. (Dockray, Nature 264, 4022, 1979).

CCK_8, the carboxyl terminal octapeptide fragment of CCK, is the smallest CCK fragment that remains fully biologically active. (Larsson and Rehfeld, Brain Res. 165, 201-218, 1979). The localization of CCK fragments in the cortex of the brain suggests that CCK may be an important neuromodulator of memory, learning and control of primary sensory and motor functions. CCK and its fragments are believed to play an important role in appetite regulation and satiety. (Della-Fera, Science 206, 471, 1979; Gibbs et al., Nature 289, 599, 1981; and Smith, Eating and Its Disorders, eds., Raven Press, New York, 67 1984).

CCK antagonists (B.J. Gertz in Neurology and Neurobiology Vol 47, Cholecystokinin Antagonists, Wang and Schoenfeld eds. Alan R. Liss, Inc., New York, NY, 327-342, 1988; Silverman et al., Am J Gastroent., 82(8), 703-8, 1987) are useful in the treatment and prevention of CCK-related disorders of the gastrointestinal (GI) (Lotti et

al., J Pharm Exp Therap., 241(1), 103-9, 1987), central nervous (CNS) (Panerai et al Neuropharmacology, 26(9), 1285-87, 1987) and appetite regulatory systems of animals, especially man. CCK antagonists are also useful in potentiating and prolonging opiate induced analgesia and thus have utility in the treatment of pain. (Faris et al., Science 226, 1215, 1984; Rovati et al., Clinical Research, 34(2), 406A, 1986; Dourish et al., European J. Pharmacology, 147, 469-72, 1988). Disease states that may be treated with CCK antagonists are disorders of gastric emptying, gastroesophageal reflux disease (Setnikar et al Arzn Forsch./Drug Research, 37(II) 10, 1168-71, 1987), pancreatitis, pancreatic and gastric carcinomas (Douglas et al., Gastroent. 96, 4629, 1989; Beauchamp et al., Am Surg. 202, 313-9, 1985), disorders of bowel motility, biliary dyskinesia, anorexia nervosa, hypoglycemia (Rossetti, Diabetes, 36, 1212-15, 1987; Reagan, European J. Pharmacology, 144, 241-3, 1987), gallbladder disease, and the like.

Previously four distinct chemical classes of CCK receptor antagonists have been reported. The first class comprises derivatives of cyclic nucleotides as represented by dibutyryl cyclic GMP (N. Barlos et al., Am. J. Physiol., 242, G161, 1982) and references sited therein). The second class is represented by the C-terminal fragments of CCK (see Jensen et al. Biochem. Biophys. Acta, 757, 250 1983) and Spanarkel J. Biol. Chem. 258, 6746, 1983). The third class comprises amino acid derivatives of glutamic acid and tryptophan as indicated by proglumide (and its analogs) and benzotript (see Hahne

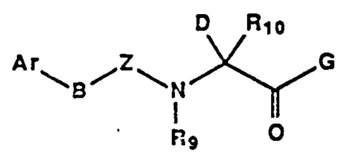
et al. Proc. Natl. Acad. Sci. U.S.A., 78, 6304, 1981 and Jensen et al. Biochem. Biophys. Acta. 761, 269, 1983). The fourth and most recent class is comprised of 3-substituted benzodiazepines, represented by L-364,718 (see: Evans et al. Proc. Natl. Acad. Sci. U.S.A., 83 4918, 1986).

With the exception of certain substituted benzodiazepines and recently reported analogs of proglumide (Makovec et al Arzneim.-Forsch./Drug Res. 36,(I), 98-102, 1986), all of these compounds are relatively weak antagonists of CCK usually demonstrating IC_{50}'s between 10^{-4} and 10^{-6} M. The benzodiazepine CCK antagonists or their metabolites may have undesireable effects *in vivo* due to their interaction with benzodiazepine or other receptors.

The C-terminal pentapeptide fragment of CCK is the same as the C-terminal pentapeptide fragment of another polypeptide hormone, gastrin. Gastrin, like CCK, exists in the GI system. Gastrin antagonists are useful in the treatment and prevention of gastrin related disorders of the GI system such as ulcers, Zollinger-Ellison syndrome and central G cell hyperplasia. There are no effective receptor antagonists of the *in vivo* effects of gastrin. (Morely, Gut Pept. Ulcer Proc., Hiroshima Symp. 2nd, 1, 1983). A recent report (Bock J. Med. Chem., 32, 13-16, 1989) discloses potent *in vitro* gastrin antagonists.

Disclosure of the Invention

In accordance with the present invention, there are cholecystokinin antagonists of the formula:



(I)

or a pharmaceutically acceptable salt thereof.

G is

(1) NH_2 or

(2) substituted amino.

R_9 is

(1) hydrogen,

(2) loweralkyl,

(3) carboxy-substituted alkyl or

(4) carboxyester-substituted alkyl.

R_{10} is

(1) hydrogen,

(2) loweralkyl,

(3) functionalized alkyl or

(4) cycloalkyl.

D is

(1) hydrogen,

(2) loweralkyl,

(3) functionalized alkyl,
(4) cycloalkyl,
(5) aryl,
(6) functionalized oxyalkyl or
(7) heterocyclic;

or R_{10} taken together with D is

(1) C_4 to C_6 alkylene,
(2) $-(CH_2)_q-V-(CH_2)_r-$ wherein q is 1 to 3, r is 1 to 3 and
V is
(i) -O-,
(ii) -S-,
(iii) $-CH_2-$ or
(iv) $-N(R_{25})-$ wherein R_{25} is hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, arylalkyl, aryl or an N-protecting group;

or R_9 taken together with D is

(1) C_3 to C_5 alkylene or
(2) $-(CH_2)_p-V-(CH_2)_t-$ wherein p is 1 to 3, t is 1 to 3 and V is defined as above.

Z is

(1) -C(O)-,
(2) -C(S)- or
(3) $-S(O)_2-$.

B is

(1) absent,
(2) alkylene,
(3) alkenylene,

(4) substituted alkenylene,

(5) $-R_{26}-R_{27}-$ wherein R_{26} is absent or $-CH_2-$ and R_{27} is -O-, -S-, -NH- or -N(loweralkyl)- or

(6) $-R_{27}-CH_2-$ wherein R_{27} is defined as above.

Ar is

(1) aryl or

(2) a heterocyclic group.

Compounds wherein D is indolylmethyl, indolinylmethyl or oxindolylmethyl are disclosed in the copending parent application PCT Patent Application Serial No. PCT/US89/01412, filed April 4, 1989.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 8 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl and the like.

The term "functionalized alkyl" as used herein includes

(1) haloalkyl,

(2) alkenyl,

(3) arylalkyl,

(4) arylalkyl wherein the alkyl group is substituted by

(i) $-OR_{16}$ wherein R_{16} is hydrogen or a hydroxyl protecting group,

(ii) $-NHR_{15}$ wherein R_{15} is hydrogen or an

N-protecting group,

(iii) $-OR_{13}$ wherein R_{13} is loweralkyl,

(iv) $-OR_{14}$ wherein R_{14} is an aryl group or

(v) $-SR_{13}$ wherein R_{13} is loweralkyl,

(5) heterocyclicalkyl,

(6) heterocyclicalkyl wherein the alkyl group is substituted by

(i) $-OR_{16}$ wherein R_{16} is hydrogen or a hydroxyl protecting group,

(ii) $-NHR_{15}$ wherein R_{15} is hydrogen or an N-protecting group,

(iii) $-OR_{13}$ wherein R_{13} is loweralkyl,

(iv) $-OR_{14}$ wherein R_{14} is an aryl group or

(v) $-SR_{13}$ wherein R_{13} is loweralkyl,

(7) loweralkyl substituted by -S-loweralkyl, -S(O)-loweralkyl or $-S(O)_2$-loweralkyl,

(8) loweralkyl substituted by -S-aryl, -S(O)-aryl or $-S(O)_2$- aryl and

(9) loweralkyl substituted by $-NHR_{12}$ wherein R_{12} is

(i) hydrogen,

(ii) $-C(O)R_4$ wherein R_4 is independently selected from loweralkyl, alkenyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl,

(iii) $-CO_2R_4$ wherein R_4 is independently defined as above,

(iv) an N-protecting group,

(v) -C(O)-A-aryl wherein A is alkenylene, substituted alkenylene, $-OCH_2-$, $-SCH_2-$, -NH-, -N(loweralkyl)-, -S- or -O-.

The term "functionalized oxyalkyl" as used herein includes $-T-OR_{11}$ wherein

T is

(1) alkylene or

(2) arylalkylene and

R_{11} is

(1) hydrogen,

(2) loweralkyl,

(3) haloalkyl,

(4) alkenyl,

(5) arylalkyl,

(6) hydroxyl protecting group,

(7) $-C(O)-(L)_s-R_4$ wherein R_4 is independently defined as above, s is 0 or 1 and

L is

(i) O,

(ii) S or

(iii) NH or

(8) -C(O)-A-aryl wherein A is independently defined as above.

The term "haloalkyl" as used herein refers to a loweralkyl radical in which one or more hydrogen atoms have been substituted by halo groups including, but not limited to, fluoromethyl, trifluoromethyl, chloroethyl, 2,2-difluorethyl, 2,3-dibromopropyl and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "cyanoalkyl" as used herein refers to a cyano group (-CN) appended to a loweralkyl radical.

The term "hydroxyalkyl" as used herein refers to a hydroxy group (-OH) appended to a loweralkyl radical.

The term "cycloalkyl" as used herein refers to an alicyclic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical including, but not limited to, cyclopropylmethyl, cyclohexylethyl and the like.

The term "carboxy-substituted alkyl" as used herein refers to a carboxy group (-COOH) appended to a loweralkyl radical.

The term "carboxyester-substituted alkyl" as used herein refers to a carboxyester group (-COOR' wherein R' is loweralkyl, cycloalkyl, aryl or arylalkyl) appended to a loweralkyl radical.

The term "alkenyl" as used herein refers to a straight or branched chain of 2 to 8 carbon atoms containing a carbon-carbon double bond including, but not limited to, vinyl, allyl, butenyl and the like.

The term "alkylene group" as used herein refers to a straight or branched chain spacer group containing 1 to 8 carbon atoms including, but not limited to, $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-(CH_2)_3-$ and the like.

The term "alkenylene group" as used herein refers to a straight or branched chain spacer group of 2 to 8 carbon atoms containing a carbon-carbon double bond including, but not limited to, $-CH=CH-$, $-C(CH_3)=CH-$, $-CH_2-CH=CH-$, $-CH(CH_3)-CH_2-CH=CH-CH_2-$ and the like.

The term "substituted alkenylene" as used herein refers to an alkenylene group substituted with one or two substituents independently selected from loweralkyl, haloalkyl, halo and cyano.

The term "cycloalkylalkylene" as used herein refers to a cycloalkyl group appended to an alkylene radical.

The term "substituted amino" as used herein includes $-N(R_1)(R_2)$ wherein R_1 and R_2 are independently selected from

(1) hydrogen,
(2) loweralkyl,
(3) haloalkyl,
(4) alkoxyalkyl,
(5) alkenyl,
(6) aryl,
(7) arylalkyl,
(8) cycloalkyl,
(9) cycloalkylalkyl,
(10) cyanoalkyl,
(11) loweralkyl substituted by $-CO_2R_3$ wherein R_3 is
  (i) hydrogen,
  (ii) loweralkyl,
  (iii) cycloalkyl,
  (iv) aryl or
  (v) arylalkyl,
(12) loweralkyl substituted by $-C(O)N(R_5)(R_6)$ wherein R_5 and R_6 are independently selected from
  (i) hydrogen,
  (ii) loweralkyl,

(iii) cycloalkyl,
(iv) alkoxyalkyl,
(v) alkenyl,
(vi) aryl and
(vii) arylalkyl,

(13) $-W-CO_2R_3$ wherein R_3 is defined as above and W is
(i) cycloalkylalkylene,
(ii) arylalkylene or
(iii) heteroarylalkylene,

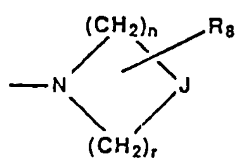
(14) adamantyl,

(15) indanyl and

(16) -CH(aryl)-X wherein X is arylalkyl;

with the proviso that R_1 and R_2 are not both hydrogen.

Substituted amino also includes



wherein n is 1 to 3, r is 1 to 3 and J is

(1) -S-,
(2) -S(O)-,
(3) $-S(O)_2-$,
(4) -O-,
(5) $-CH_2-$,
(6) $-N(R_5)-$ wherein R_5 is defined as above or
(7) $-N(C(O)R_4)$ wherein R_4 is defined as above and

R_8 represents one, two or three substituents independently

selected from

(1) hydrogen,

(2) loweralkyl,

(3) haloalkyl,

(4) aryl,

(5) $-C(O)R_4$ wherein R_4 is independently defined as above,

(6) $-C(O)N(R_5)(R_6)$ wherein R_5 and R_6 are independently defined as above,

(7) $-OR_{16}$ wherein R_{16} is

(i) hydrogen or

(ii) hydroxyl protecting group,

(8) hydroxyalkyl,

(9) alkoxyalkyl,

(10) $-NH(R_{15})$ wherein R_{15} is

(i) hydrogen or

(ii) an N-protecting group,

(11) cyano and

(12) halo.

The term "alkylamino" as used herein refers to $-NHR_{40}$ wherein R_{40} is a loweralkyl group.

The term "dialkylamino" as used herein refers to $-NR_{41}R_{42}$ wherein R_{41} and R_{42} are independently selected from loweralkyl.

The term "aminocarbonyl" as used herein refers to $-C(O)NH_2$.

The term "alkylaminocarbonyl" as used herein refers to $-C(O)R_{50}$ wherein R_{50} is an alkylamino group.

The term "dialkylaminocarbonyl" as used herein refers to $-C(O)R_{51}$ wherein R_{51} is a dialkylamino group.

The term "alkenylaminocarbonyl" as used herein refers to $-C(O)NHR_{52}$ wherein R_{52} is an alkenyl group.

The term "halogen" or "halo" as used herein refers to F, Cl, Br, I.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{13}O-$ and $R_{13}S-$ respectively, wherein R_{13} is a loweralkyl group.

The term "alkoxycarbonyl" as used herein refers to $-C(O)OR_{43}$ wherein R_{43} is loweralkyl.

The term "aryl" or "aryl group" as used herein refers to a monocyclic, bicyclic or tricyclic carbocyclic ring system containing one or more aromatic carbocyclic rings including, but not limited to, phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl, isoindenyl and the like. Aryl groups can be unsubstituted or substituted with one, two, or three substituents independently selected from loweralkyl, alkoxy, thioalkoxy, carboxy, alkoxycarbonyl, arylcarbonyloxy, arylalkylcarbonyloxy, heterocycliccarbonyloxy, heterocyclicalkylcarbonyloxy, arylalkoxy, heterocylicalkoxy, $-OSO_3H$, cyano, nitro, haloalkyl, hydroxy, amino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkenylaminocarbonyl, alkylamino and dialkylamino.

The term "arylalkyl" as used herein refers to an aryl group appended to a loweralkyl radical.

The term "arylalkylene" as used herein refers to an aryl group appended to an alkylene radical.

The term "arylcarbonyloxy" as used herein refers to $R_{54}C(O)O-$ wherein R_{54} is an aryl group.

The term "arylalkylcarbonyloxy" as used herein refers to $R_{55}C(O)O-$ wherein R_{55} is an arylalkyl group.

The term "arylalkoxy" as used herein refers to $R_{56}O-$ wherein R_{56} is an arylalkyl group.

The term "heteroaryl" as used herein refers to a monocyclic or bicyclic aromatic ring system, each ring having 5 or 6 atoms, one to four of which are independently selected from oxygen, sulfur and nitrogen. Heteroaryl groups also include a heteroaryl ring as defined above fused to a benzene ring. Heteroaryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, hydroxy, cyano, nitro, haloalkyl, alkoxy, thioalkoxy, amino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkenylaminocarbonyl, alkylamino, dialkylamino, N-protected amino, protected hydroxyl, carboxylic acid, carboxamide, arylcarbonyloxy, arylalkylcarbonyloxy, heterocycliccarbonyloxy, heterocyclicalkylcarbonyloxy, arylalkoxy, heterocylicalkoxy, $-OSO_3H$, carbamyl and aryl.

The term "heteroarylalkyl" as used herein refers to a heteroaryl group appended to a loweralkyl radical.

The term "heteroarylalkylene" as used herein refers to a heteroaryl group appended to an alkylene radical.

The term "heterocyclic ring" or "heterocyclic" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5- or 6-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom. The 5-membered ring has 0-2

double bonds and the 6-membered ring has 0-3 double bonds. The nitrogen and sulfur heteroatoms can be optionally oxidized. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" includes any bicyclic or tricyclic group wherein the heterocyclic ring is fused to one or two benzene rings or one or two heterocyclic groups independently defined as above. Heterocyclics include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, and the like. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, oxo, hydroxy, protected hydroxyl, alkoxy, thioalkoxy, amino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkenylaminocarbonyl, alkylamino, dialkylamino, N-protected amino, cyano, nitro, carboxylic acid, carboxamide, arylcarbonyloxy, arylalkylcarbonyloxy, heterocycliccarbonyloxy, heterocyclicalkylcarbonyloxy, arylalkoxy, heterocylicalkoxy, $-OSO_3H$, carbamyl and aryl.

The term "heterocyclicalkyl" as used herein refers to a heterocyclic group appended to a loweralkyl group.

The term "heterocycliccarbonyloxy" as used herein refers to $R_{57}C(O)O-$ wherein R_{57} is a heterocyclic group.

The term "heterocyclicalkylcarbonyloxy" as used herein refers to $R_{58}C(O)O-$ wherein R_{58} is a heterocyclicalkyl group.

The term "heterocyclicalkylene" as used herein refers to a heterocyclic group appended to an alkylene radical.

The term "heterocyclicalkoxy" as used herein refers to $R_{59}O-$ wherein R_{59} is a heterocyclicalkyl group.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the compounds or to increase the solubility of the compounds and includes, but is not limited to, sulfonyl, acyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), benzoyl or an α-aminoacyl residue, which may itself be N-protected similarly.

The term "hydroxyl protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures and includes, but is not limited to, substituted methyl ethers, for example methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyl, and triphenylmethyl; terahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl and t-butyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and

t-butyldiphenylsilyl; cyclic acetals and ketals, for example, methylene acetal, acetonide and benzylidene acetal; cyclic ortho esters, for example, methoxymethylene; cyclic carbonates; cyclic boronates; and esters, for example acetates or benzoates.

Exemplary compounds of the present invention include:
N-(3'-Quinolylcarbonyl)-R-Valine-di-n-pentylamide;
N-(2'-Indolylcarbonyl)-R-Valine-di-n-pentylamide;
N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-Valine-di-n-pentylamide;
N-(2'-Naphthoyl)-R-Valine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Norleucine-di-n-pentylamide;
N-(2'-Indolylcarbonyl)-R-Norleucine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl-R-(O-benzyl)Serine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-benzyl)Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-(2R,3S)-Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-acetyl)Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-methyl)Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-3-(2'-thienyl)-R-Alanine-di-n-pentylamide;
N-(2'-Indolylcarbonyl)-R-Histidine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Histidine-di-n-pentylamide;
N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(benzyloxycarbonyl)-R-Lysine-di-n-pentylamide;

N-(3'-Quinolylcarbonyl)-R-Phenylalanine-di-n-pentylamide;
N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(2'-chlorobenzyloxycarbonyl)-R-Lysine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-(4'-hydroxyphenyl)glycine-di-n-pentylamide;
N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(acetyl)-R-Lysine-di-n-pentylamide;
N-(2'-Indolylcarbonyl)-R-Tyrosine-di-n-pentylamide;

N-(3',4'-Dichlorobenzoyl)-R-Tyrosine-di-n-pentylamide;
N-(2'-Naphthoyl)-R-Tyrosine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Tyrosine-di-n-pentylamide;
Methyl N-(3'-Quinolylcarbonyl)-R-Tyrosyl-S-phenylglycinate;
N-(2'-Indolylcarbonyl)-R,S-Homoserine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R,S-Homoserine-di-n-pentylamide;
N-(2'-Indolylcarbonyl)-R-Methioninesulfoxide-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Methionine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Methioninesulfoxide-di-n-pentylamide;
N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-phenylthiolcarbonyl-R-Lysine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Tyrosine-di-n-pentylamide hydrochloride;
N-(3'-Quinolylcarbonyl)-R-Histidine-di-n-pentylamide dihydrochloride;
N-(2'-Indolylcarbonyl)-glycine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)glycine-di-n-pentylamide;
N-(3'Quinolylcarbonyl)-R-phenylglycine-di-n-pentylamide;

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-Phenylglycine-di-n-pentylamide;

N-(5'-Fluoroindolylcarbonyl)-R-phenylglycine-di-n-pentylamide;

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)glycine-di-n-pentylamide;

N-(2'-Naphthoyl)glycine-di-n-pentylamide;

N-(3'-Methylphenylaminocarbonyl)glycine-di-n-pentylamide;

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-(4'-hydroxyphenyl)-glycine-di-n-pentylamide;

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-(2R,3S)-(O-benzyl)-Threonine-di-n-pentylamide;

Methyl N-(3'-Quinolylcarbonyl)-R-Methionine-S-(p-hydroxy)-phenylglycinate;

N-(3'-Quinolylcarbonyl)-R-Serine-di-n-pentylamide;

N-(8'-Hydroxy-2-quinolylcarbonyl)-glycine-di-n-pentylamide;

N-Methyl-N-(3'Quinolylcarbonyl)-glycine-di-n-pentylamide;

N-(3'-Iodo-2'-indolylcarbonyl)-glycine-di-n-pentylamide; and

N-(2'-Indolylcarbonyl)-R-Alanine-di-n-pentylamide.

The compounds of the invention may be made as shown in the following scheme(s). The compounds of the invention having one asymmetric center can exist as separate enantiomers or as mixtures of enantiomers. The compounds of the invention which contain two or more asymmetric carbon atoms can exist as pure diastereomers, mixtures of distereomers, diastereomeric racemates or mixtures of diastereomeric racemates. The present

invention includes within its scope all of the isomeric forms.

A number of synthetic pathways exist for the production of α-amino acids and their derivatives. The invention is not limited to those methods discussed here for the synthesis of α-amino acids but is meant to include those variations and methods encompassed by the prior art as discussed in the chemical literature in its entirety. α-Amino acids (refer to Scheme 1) can be produced directly by the displacement of α-halogenated esters (**1**, X is halo) and the like or other α-situated leaving groups by ammonia and or other substituted amines (R_9 is hydrogen, loweralkyl, carboxyester-substituted alkyl) and/or their analogs (e.g., carbamates, hydrazines, azides) (e.g., Marvel Org Synth 20, 81, **1940**; 106, **1940**; 21, 60, **1941**; 74, **1941**; Birnbaum, J Biol Chem, 333, **1953**). The amino group is then unmasked, for example by reduction, and the ester group (amide, etc.) is saponified to the acid in a standard fashion.

A second method involves the condensation of an α-ketoester (amide, etc) with an amine or amine equivalent (e.g., hydroxylamine, hydrazine, carbamate, etc.) and the subsequent reduction of this product (**2**) to the α-aminoester (amide, acid, etc. (e.g., Can J Chem, 29, 427, **1951**; J Org Chem, 38, 822, **1973**; J Org Chem, 6, 878, **1941**)). Alternatively, an organometalic reagent can be added to the oxime **2** (imine, etc.) to provide as final products either monosubstituted α-amino acids in the case where D is hydrogen, or disubstituted amino acids in the

case where D is other than hydrogen (e.g., Tetrahedron Lett, 28(42), 4973, 1987).

A third method is the alkylation of a carbanion resulting from compound (3) with an electrophilic nitrogen source (eg. diethylazodicarboxylate). The intermediate product can subsequently be unmasked to provide the desired α-amino acid. A similar method involves alkylation of the carbanion derived from compound (4) with an appropriate alkylating agent. This method also allows for the possibility of disubstitution of the α center.

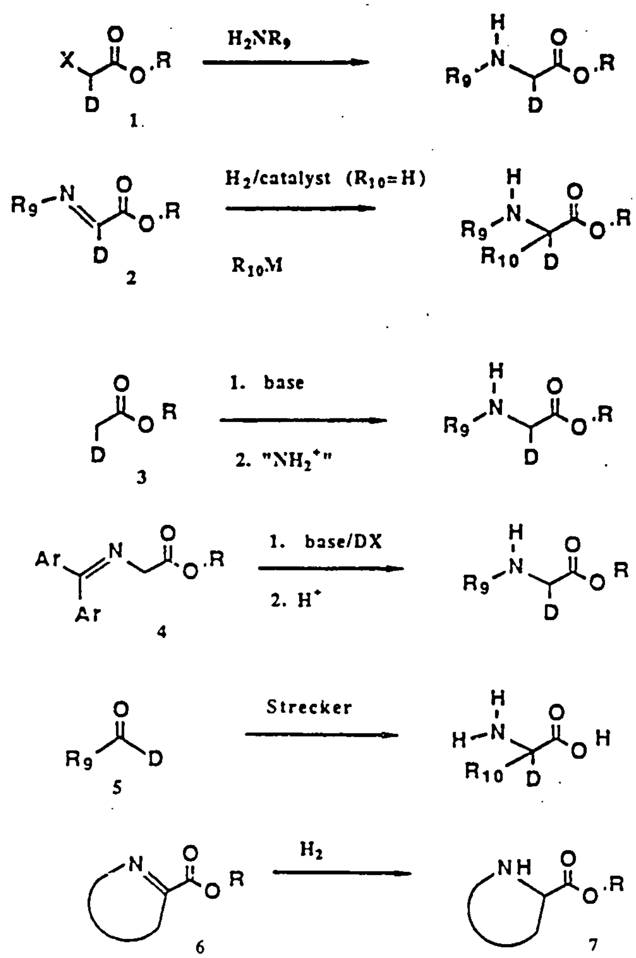
A fifth route involves the Strecker reaction and its modifications. Reaction of cyanide and ammonium on aldehydes and ketones (5) provides the amino acid.

A last method involves the direct reduction of unsaturated heterocyclic carboxylic acids (6) to directly provide the cyclic amino acids (7), (wherein D and R_9 are encompassed in a ring).

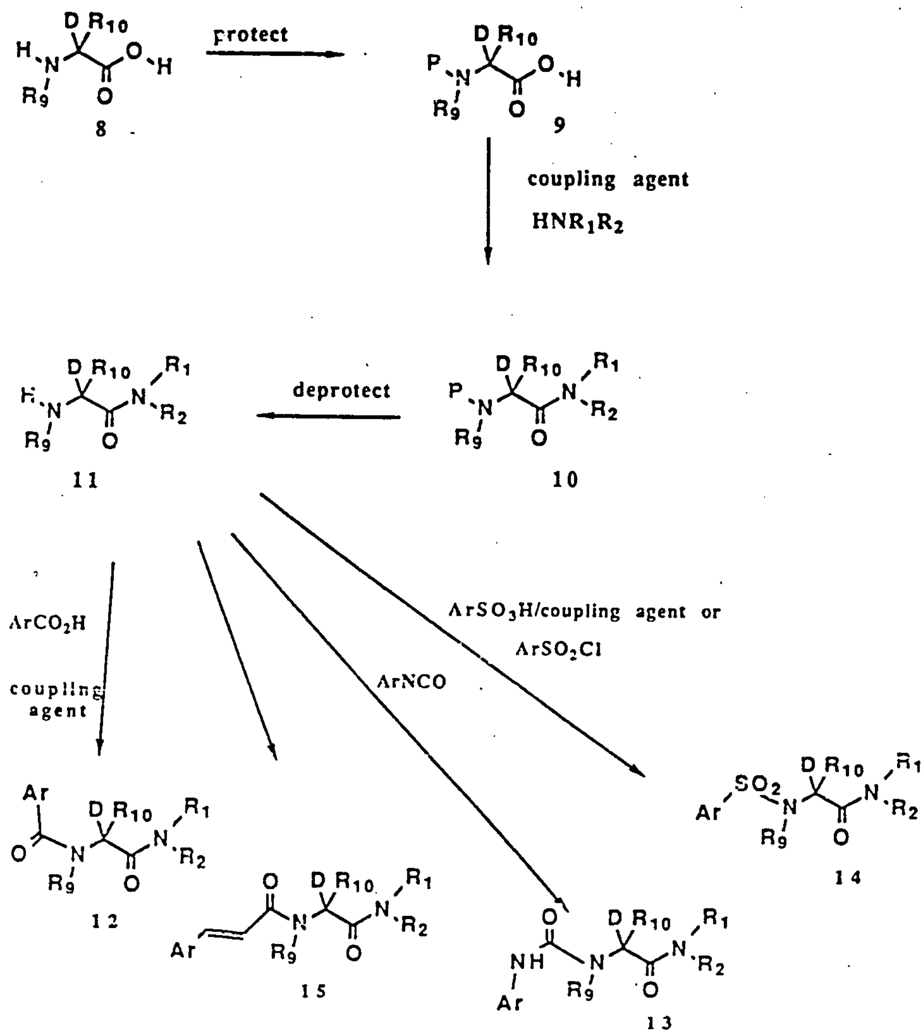
With suitably available α-amino acids (8) (Scheme 2) the amino group is protected with an N protecting group (most frequently Boc or Cbz) and, if the carboxylic acid has not been unmasked, it is saponified with base to provide the parent carboxylic acid (9). The N-protected intermediate is then coupled with the amine HNR_1R_2 using any of a number of standard coupling techniques (carbodiimide, BOPCl, chloroformates, oxalylchloride, etc.). Preferred secondary amines are of the type where R_1 and R_2 are alkyl, arylalkyl, aryl, or represent another amino acid. The resulting product (10) is then N-deprotected using HCl or trifluoroacetic acid to remove a Boc group and hydrogenolysis or HBr to remove a Cbz group.

The resultant amine (11) is then coupled with aromatic carboxylic acids, aromatic acid halides, heteroaromatic carboxylic acids, aromatic isocyanates, aromatic sulfonic acids, aromatic sulfonyl chlorides, and the like using standard coupling techniques to provide the desired products (12), (13), (14), and (15). Preferred acyl coupling partners groups include: quinoline carboxylic acids, indole carboxylic acids, substituted benzoic acids and benzoyl chlorides, arylisocyanates and arylisothiocyanates, naphthoic acids, benzothiofuranyl carboxylic acids and the like.

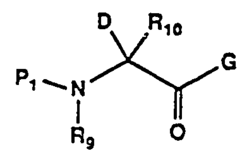
Scheme 1


H₂NR₉
H₂/catalyst (R₁₀=H)
R₁₀M
1. base
2. "NH₂⁺"
1. base/DX
2. H⁺
Strecker
H₂
1
2
3
4
5
6
7

Scheme 2



Intermediates for the preparation of the compounds of formula I include compounds of the formula:



wherein G is
(1) NH_2 or
(2) substituted amino;
R_9 is
(1) hydrogen,
(2) loweralkyl,
(3) carboxy-substituted alkyl or
(4) carboxyester-substituted alkyl;
R_{10} is
(1) hydrogen,
(2) loweralkyl,
(3) functionalized alkyl or
(4) cycloalkyl;
D is
(1) hydrogen,
(2) loweralkyl,
(3) functionalized alkyl,
(4) cycloalkyl,
(5) aryl,
(6) functionalized oxyalkyl or
(7) heterocyclic;
or R_{10} taken together with D is
(1) C_4 to C_6 alkylene,

(2) $-(CH_2)_q-V-(CH_2)_r-$ wherein q is 1 to 3, r is 1 to 3 and

V is

(i) -O-,

(ii) -S-,

(iii) $-CH_2-$ or

(iv) $-N(R_{25})-$ wherein R_{25} is hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, arylalkyl, aryl or an N-protecting group;

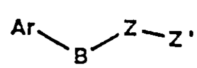
or R_9 taken together with D is

(1) C_3 to C_5 alkylene or

(2) $-(CH_2)_p-V-(CH_2)_t-$ wherein p is 1 to 3, t is 1 to 3 and V is defined as above; and

P_1 is hydrogen or an N-protecting group.

Other intermediates for the preparation of compounds of the formula I include compounds of the formula:



wherein Z is

(1) -C(O)-,

(2) -C(S)- or

(3) $-S(O)_2-$;

B is

(1) absent,

(2) alkylene,

(3) alkenylene,

(4) substituted alkenylene,

(5) $-R_{26}-R_{27}-$ wherein R_{26} is absent or $-CH_2-$ and R_{27} is -O-, -S-, -NH- or -N(loweralkyl)- or

(6) $-R_{27}-CH_2-$ wherein R_{27} is defined as above;

Ar is

(1) aryl or

(2) a heterocyclic group; and

Z' is an activating group; or B-Z-Z' taken together represent -N=C=O, -N=C=S, $-CH_2-N=C=O$ or $-CH_2-N=C=S$.

Activating groups are those functional groups which activate a carboxylic acid or sulfonic acid group toward coupling with an amine to form an amide or sulfonamide bond. Activating groups Z' include, but are not limited to, -OH, -SH, alkoxy, thioalkoxy, halogen, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 4-nitrophenol derived esters, 2,4,5-trichlorophenol derived esters and the like.

The following examples will serve to further illustrate preparation of the novel compounds of this invention.

Example 1

N-(t-Butyloxycarbonyl)-R-Valine-di-n-pentylamide

N-t-Butyloxycarbonyl-R-Valine (2.5 g, 11.5 mmol) was stirred at $0^{\circ}C$ in 30 mL of methylene chloride (CH_2Cl_2) with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 3.5 g, 13.8 mmol) and 1.5 mL (11.5 mmol) of triethylamine (TEA). To this reaction mixture was added di-n-pentylamine (11.6 mL, 58 mmol). The mixture was stirred overnight and allowed to warm to room temperature.

An additional equivalent of BOPCl was added after 18 hrs and the reaction mixture was stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate (EtOAc) and washed with water, 1 N hydrochloric acid (HCl) solution, saturated sodium bicarbonate solution ($NaHCO_3$), water. The organic solution was dried over magnesium sulfate ($MgSO_4$). After filtration and concentration of the filtrate in vacuo, the residue was chromatographed using ethyl acetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil 79% yield (3.25 g). $[\alpha]_D = +21.2^{\circ}$ (c=1.5, MeOH). MS(CI) m/e 357(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85-1.0(m,12H), 1.32(m,8H), 1.4-1.5(m,4H), 1.5(s,9H), 1.84(m,1H), 3.05(m,1H), 3.2(m,1H), 3.35(m,1H), 3.55(m,1H), 4.42(m,1H), 5.25(d,J=7Hz,1H).

Example 2

R-Valine-di-n-pentylamide hydrochloride

The product of example 1 (0.2 g, 0.6 mmol) was dissolved in 4 N HCl in dioxane (10 mL) and stirred under inert atmosphere (N_2) for an hour. When the reaction was complete by tlc the solvents were evaporated in vacuo and hexane and diethylether were added. The residue was triturated with these two solvents and the solvents again evaporated in vacuo. This procedure was repeated several times until product was obtained as a glass in quantitative yield. MS(CI) m/e 293(m+H)$^+$.

Example 3

N-(3'-Quinolylcarbonyl)-R-Valine-di-n-pentylamide

The hydrochloride of example 2 (150 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 100 mg), HOBt (135 mg) and quinoline-3-carboxylic acid (88 mg) were stirred at $0^{o}C$ under nitrogen in 5 mL of anhydrous CH_2Cl_2. To this mixture was added 120 µL of N-methylmorpholine (NMM) and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethyl acetate and water and the organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed using ethylacetate (EtOAc) and hexane as the elutant mixture to provide 110 mg of an oil (54% yield) after removal of the volatiles. $[\alpha]_D$= -14.8° (c=0.5, MeOH). MS(CI) m/e 412(m+H)$^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.92(m,6H), 1.05(m,6H), 1.35(m,8H), 1.5-1.7(m,4H), 2.15(m,1H), 3.05(m,1H), 3.3-3.4(m,1H), 3.5(m,1H), 3.65(m,1H), 5.08(dd,J=3,9Hz,1H), 7.25(d,J=9Hz,1H), 7.62(t,J=7Hz,1H), 7.8(t,J=7Hz,1H), 7.91(d,J=10Hz,1H), 8.16(d,J=10Hz,1H), 8.6(d,J=3Hz,1H), 9.35(d,J=3Hz,1H). Analysis calculated for $C_{25}H_{37}N_3O_2$: C 72.95, H 9.06, N 10.21; found: C 72.61, H 9.21, N 9.97.

Example 4

N-(2'-Indolylcarbonyl)-R-Valine-di-n-pentylamide

The hydrochloride of example 2 (130 mg, 0.45 mmol), EDCI (90 mg), HOBt (120 mg) and indole-2-carboxylic acid

(75 mg) were stirred at 0°C under nitrogen in 5 mL of anhydrous CH_2Cl_2. To this mixture was added 100 µL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethylacetate and water and the organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed using ethylacetate and hexane as the elutant mixture to provide 36 mg of product (75% yield) after evaporation of the volatiles. mp= 132-4°C. $[\alpha]_D$= -9.2° (c=0.5, MeOH). MS(CI) m/e 400(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(t,J=7Hz,6H), 1.0(m,6H), 1.2-1.4(m,8H), 1.5-1.6(m,4H), 2.12(m,1H), 3.05(m,1H), 3.3(m,1H), 3.42(m,1H), 3.63(m,1H), 5.0(q,J=3,6Hz,1H), 7.0(m,1H), 7.1(d,J=9Hz,1H), 7.25(t,J=7.5Hz,1H), 7.3(t,J=7.5Hz,1H), 7.41(d,J=7Hz,1H), 7.65(d,J=7Hz,1H), 9.3(bs,1H). C,H,N analysis calculated for $C_{24}H_{37}N_3O_2$: C 72.14, H 9.34, N 10.52; found: C 72.52, H 9.25, N 10.49.

Example 5

N-(2'-Quinolylcarbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 0.2 g of the hydrochloride salt of example 2, quinoline-2-carboxylic acid (0.12 g), EDCI (0.15 g), HOBt (0.1 g), and NMM (0.18 mL). The product was isolated in 80% yield (0.225 g). mp= 78-79°C. $[\alpha]_D$= -13.1° (c=1.1, MeOH). MS(CI) m/e 412(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.05(m,6H), 1.2-1.4(m,8H), 1.55(m,4H), 2.22(m,1H), 3.08(m,1H), 3.4(m,2H), 3.64(m,1H),

5.0(dd,J=3,7Hz,1H), 7.62(t,J=7Hz,1H), 7.78(t,J=7Hz,1H), 7.85(d,J=9Hz,1H), 8.15(d,J=9Hz,1H), 8.35(m,2H), 8.85(d,J=10Hz,1H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_2$, H_2O: C 72.17, H 8.96, N 10.10; found: C 72.36, H 8.93, N 10.03.

Example 6

N-[E-2'-Cyano-3'-(4''-hydroxyphenyl)prop-2'-enoyl]-R-Valine-di-n-pentylamide

The hydrochloride of example 2 (300 mg, 1.03 mmol), EDCI (200 mg), HOBt (280 mg) and α-cyano-4-hydroxycinnamic acid (195 mg) were stirred at 0°C under nitrogen in 15 mL of anhydrous CH_2Cl_2. To this mixture was added 250 μL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethylacetate and water and the organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed using ethylacetate and hexane as the elutant mixture to provide 225 mg of an oily product (57% yield) after evaporation of the volatiles. $[\alpha]_D = -4.8^\circ$ (c=1.15, MeOH) MS(CI) m/e 428(m+H)$^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.92(m,6H), 1.08(m,6H), 1.35(m,8H), 1.56-1.75(m,4H), 2.15(m,1H), 3.1(m,1H), 3.3-3.5(m,2H), 3.7(m,1H), 4.65(m,1H), 6.73(d,J=9Hz,1H), 6.85(d,J=9Hz,2H), 7.65(d,J=9Hz,2H), 7.72(s,1H), 9.28(s,1H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_3$: C 70.22, H 8.72, N 9.83; found: C 69.88, H 8.39, N 9.60.

Example 7

N-(2'-Benzothiofuranylcarbonyl)-R-Valine-di-n-pentylamide.

The reaction was performed in a similar manner to that in example 3 utilizing 0.3 g of the hydrochloride salt of example 2, benzothiofuran-2-carboxylic acid (0.205 g), EDCI (0.22 g) HOBt (0.28 g), and NMM (0.22 mL). The oily product was isolated in 58% yield, 0.28 g $[\alpha]_D = -5.85^\circ$ (c=2.0, MeOH). MS(CI) m/e 417(m+H)$^+$, 158. ^1H NMR($CDCl_3$,300MHz) δ 0.9-1.1(m,12H), 1.2-1.3(m,8H), 1.5-1.6(m,4H), 2.15(m,1H), 3.05(m,1H), 3.3(m,1H), 3.42(m,1H), 3.65(m,1H), 5.0(q,J=3,6Hz,1H), 7.00(d,J=9Hz,1H), 7.41(m,2H), 7.80(s,1H), 7.86(m,2H). C,H,N analysis calculated for $C_{24}H_{36}N_2O_2S$, 0.25 H_2O: C 68.45, H 8.74, N 6.65; found: C 68.73, H 8.48, N 6.71.

Example 8

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-Valine-di-n-pentylamide

The hydrochloride salt of example 2 (0.95 g, 3.22 mmol) was stirred in 25 mL of CH_2Cl_2 with NMM (0.7 mL) under nitrogen at $0^\circ C$. EDCI (0.7 g) and HOBt (0.11 g) were added followed by the addition of 4,8-dihydroxyquinoline-2-carboxylic acid (0.66 g, 3.22 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, 0.1 N solution of HCl, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using

ethylacetate, hexane and methanol as the elutant mixture. The product was crystallized from methanol-water to provide 0.82 g (56%). mp= 233-235^{o}C. $[\alpha]_D$ = -15.6^{o} (c=0.5, MeOH). MS(CI) m/e 444(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.84(m,6H), 0.92(m,6H), 1.1-1.35(m,8H), 1.4-1.6(m,4H), 2.33(m,1H), 3.1-3.45(m,2H), 3.55(m,2H), 4.67(m,1H), 7.1(d,J=9Hz,1H), 7.42(t,J=7Hz,1H), 7.55(m,2H), 9.62(d,J=9Hz,1H), 10.3(s,1H), 11.75(s,1H). C,H,N calculated for $C_{25}H_{37}N_3O_4$: C 67.69 H 8.41, N 9.47; found: C 67.47 H 8.45, N 9.39.

Example 9

N-(2'-Benzofuranylcarbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 0.3 g of the hydrochloride salt of example 2, benzofuran-2-carboxylic acid (0.19 g), EDCI (0.22 g), HOBt (0.28 g), and NMM (0.22 mL). Product was isolated in 56% yield (0.225 g). $[\alpha]_D$= -29.2^{o} (c=1.1, MeOH). MS(CI) m/e 401(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9-1.0(m,6H), 1.05(m,6H), 1.25-1.4(m,8H), 1.5-1.68(m,4H), 2.15(m,1H), 3.1(m,1H), 3.28-3.5(m,2H), 3.62(m,1H), 5.0(dd,J=3,6Hz,1H), 7.28(t,J=8Hz,1H), 7.4(t,J=8Hz,2H), 7.45(s,1H), 7.52(d,J=9Hz,1H), 7.65(d,J=9Hz,1H). C,H,N analysis calculated for $C_{24}H_{36}N_2O_3$: C 71.96, H 9.06, N 6.99; found: C 72.09, H 9.08, N 6.99.

Example 10

N-[4'-Hydroxy-2'-phenyl-3'-quinolylcarbonyl]-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 0.2 g of the hydrochloride salt of example 2, 4-hydroxy-2-phenyl-quinoline-3-carboxylic acid (0.18 g), EDCI (0.16 g), HOBt (0.19 g), and NMM (0.16 mL). Product was isolated in 64% yield (0.22 g). mp= 154-155°C. $[\alpha]_D$ = -30.0° (c=0.4, MeOH). MS(CI) m/e 504(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.82(m,14H), 1.2(m,8H), 1.38(m,4H), 1.94(m,1H), 3.02(m,2H), 3.2(m,1H), 3.4(m,1H), 4.55(m,1H), 7.43(m,5H), 7.7(m,2H), 8.2 (d,J=7Hz,1H), 12.02(s,1H). C,H,N analysis calculated for $C_{31}H_{41}N_3O_3$: C 73.93, H 8.21, N 8.34; found: C 73.73, H 8.18, N 8.34.

Example 11

N-(4'-Hydroxy-7'-trifluoro-3'-quinolylcarbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 0.21 g of the hydrochloride salt of example 2, 4-hydroxy-7-trifluoro-quinoline-3-carboxylic acid (0.185 g), EDCI (0.15 g), HOBt (0.2 g), and NMM (0.16 mL). Product was isolated in 37% yield, 0.16 g. mp= 194-195°C. $[\alpha]_D$ = -79.2° (c=0.5, MeOH). MS(CI) m/e 497(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.88(m,12H), 1.35(m,8H), 1.45(m,2H), 1.6(m,2H), 2.05(m,1H) 3.0(m,2H), 3.25-3.4(m,2H), 3.48(m,1H), 4.85(dd,J=3,9Hz,1H), 7.8(d,J=7Hz,1H), 8.1(s,1H), 8.45(d,J=7Hz,1H), 8.9(s,1H), 10.2(d,J=7Hz,1H), 12.9(bs,1H)

C,H,N analysis calculated for $C_{26}H_{26}F_3N_3O_3$, 0.2 H_2O: C 62.56, H 7.35, N 8.41; found: C 62.57, H 7.17, N 8.38.

Example 12

N-(7'-Chloro-4'-hydroxy-3'-quinolylcarbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 5.0 g of the hydrochloride salt of example 2, 4-hydroxy-7-chloro-quinoline-3-carboxylic acid (3.8 g), EDCI (3.5 g), HOBt (4.6 g), and NMM (3.8 mL) and 10 mL DMF. Product was isolated in 54% yield, 4.25 g. mp= 205-206°C. $[\alpha]_D$ = -93.8° (c=0.5, MeOH). MS(CI) m/e 463(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.95(m,6H), 1.15(d,J=8Hz,3H), 1.26(d,J=8Hz,3H), 1.38(m,8H), 1.65(m,2H), 1.8(m,1H), 2.0(m,1H), 2.23(m,1H), 3.15(m,1H), 3.35(m,1H), 3.48(m,1H), 3.72(m,1H), 4.6(t,J=6Hz,1H), 7.2(dd,J=3,9Hz,1H), 7.6(d,J=9Hz,1H) 7.68(d,J=2Hz,1H), 8.26(d,J=7Hz,1H), 10.25(d,J=6Hz,1H), 12.25(d,J=9Hz,1H). C,H,N analysis calculated for $C_{25}H_{36}ClN_3O_3$: C 64.98, H 7.85, N 9.09, Cl 7.67; found: C 65.16, H 8.04, N 8.94, Cl 7.91.

Example 13

N-(4'-Hydroxy-2'-quinolylcarbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 0.2 g of the hydrochloride salt of example 2, 4-hydroxyquinoline-2-carboxylic acid (0.13 g) EDCI (0.14 g), HOBt (0.19 g), and NMM (0.15 mL). Product was isolated in 71% yield (0.207 g). mp= 70-

$71^{o}C$. $[\alpha]_D = -13.3^{o}$ (c=0.6, MeOH). MS(CI) m/e 428(m+H)$^{+}$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.85-1.1(m,12H), 1.2-1.4(m,8H), 1.5-1.7(m,4H), 2.15(m,1H), 3.02(m,1H), 3.25(m,1H), 3.45(m,1H), 3.64(m,1H), 4.95(dd,J=3,6Hz,1H), 6.7(bs,1H), 7.35-7.5(m,2H), 7.65(t,J=7Hz,2H), 8.35(d,J=8Hz,1H), 10.4(bs,1H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_3$: C 70.22, H 8.72, N 9.83; found: C 69.91, H 8.71, N 9.68.

Example 14

N-[5'-(N-Allylcarbamyl)pyridyl-3'-carbonyl]-R-Valine-di-n-pentylamide

The hydrochloride salt of example 2 (0.20 g, 0.69 mmol) was stirred in 15 mL of CH_2Cl_2 with NMM, (0.15 mL, 1.4 mmol) under nitrogen at $0^{o}C$. EDCI (0.135 g, 0.69 mmol) and HOBt (0.19 g, 0.14 mmol) were added followed by the addition of 5-allylcarbamylnicotinic acid (0.142 g, 0.69 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water, and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The oily product was isolated in 56% yield (0.17 g). MS(CI) m/e 445 (m+H)$^{+}$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85-1.1(m,12H), 1.2-1.4(m,8H), 1.5-1.6(m,4H), 2.1(m,1H), 3.05(m,1H), 3.3(m,1H), 3.48(m,1H), 3.65(m,1H), 4.15(m,2H), 5.0(dd,J=3,6Hz,1H), 5.25(m,2H), 5.95(m,1H), 6.45(m,1H),

7.15(d,J=9Hz,1H), 8.48(s,1H), 9.15(s,2H). C,H,N analysis calculated for $C_{25}H_{40}N_4O_3$: C 67.53, H 9.07, N 12.60; found: C 67.27, H 8.97, N 12.53.

Example 15

N-(1'-Ethyl-7'-methyl-4'-oxo-1',8'-naphthyridinyl-3'-carbonyl)-R-Valine-di-n-pentylamide

The hydrochloride salt of example 2 (0.2 g, 0.69 mmol) was stirred in 15 mL of CH_2Cl_2 with NMM (0.15 mL, 1.4 mmol) under nitrogen at $0^{o}C$. EDCI (0.135 g, 0.69 mmol) and HOBt (0.190 g, 1.38 mmol) were added followed by the addition of nalidixic acid (0.160 g, 0.69 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue was taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The purification provided 0.19 g (59%) of an oil. MS(CI) m/e 471$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H) 1.05(m,3H), 1.20-1.4(m,10H), 1.48-1.8(m,8H), 2.1(m,1H), 2.65(s,3H), 3.05(m,1H), 3.4(m,2H), 3.6(m,1H), 4.5(dd,J=3,9Hz,1H), 4.6(m,1H), 4.95(dd,J=3,6Hz,1H), 7.25(m,2H), 8.68(m,1H), 8.85(m,1H). C,H,N analysis calculated for $C_{27}H_{42}O_3N_4$, 0.25 H_2O: C 68.34, H 9.03, N 11.82; found: C 68.12, H 8.83, N 12.07.

Example 16

N-[Z-2'-Fluoro-3'-phenylprop-2'-enoyl]-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 0.27 g of the hydrochloride salt of example 2, α-fluorocinnamic acid (0.16 g), EDCI (0.19 g), HOBt (0.25 g), and NMM (0.21 mL). The oily product was isolated in an 68% yield, 0.25 g $[\alpha]_D = +7.1^{\circ}$ (c=1.1, MeOH). MS(CI) m/e 405$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.82-1.0(m,12H), 1.2-1.5(m,8H), 1.5-1.7(m,4H), 2.1(m,1H), 3.05(m,1H), 3.25(m,1H), 3.4(m,1H), 3.6(m,1H), 4.85(m,1H), 7.05(d,J=42Hz,1H), 7.1(d,J=10Hz,1H), 7.3-7.45(m,3H), 7.62(d,J=9Hz,2H). C,H,N analysis calculated for $C_{24}H_{37}FO_2N_2$: C 71.25, H 9.22, N 6.93; found: 70.99, H 9.14, N 6.95.

Example 17

N-(2'-Naphthoyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 0.2 g of the hydrochloride salt of example 2, 2-naphthoic acid (0.12 g), EDCI (0.13 g), HOBt (0.18 g), and NMM (0.16 mL). The product was isolated as an oil in 72% yield, 0.2 g. $[\alpha]_D = -13.0^{\circ}$ (c=1.0, MeOH). MS(CI) m/e 411$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.8-0.9(m,6H), 1.1(m,6H), 1.2-1.4(m,8H), 1.55-1.67(m,4H), 2.13(m,1H), 3.0-3.1(m,1H), 3.25-3.3(m,1H), 3.5(m,1H), 3.65(m,1H), 5.08(dd,J=3,6Hz,1H), 7.11(d,J=9Hz,1H), 7.52(m,2H), 7.9(m,4H), 8.33(s,1H). C,H,N analysis calculated for

$C_{26}H_{38}N_2O_2$: C 76.05, H 9.33, N 6.82; found: C 76.20, H 9.32, N 6.98.

Example 18

N-[3'-(3''-Pyridyl)prop-2'-enoyl]-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 0.3 g of the hydrochloride salt of example 2, 3-(3'-pyridyl)acrylic acid (0.17 g), EDCI (0.22 g), HOBt (0.28 g), and NMM (0.22 mL). An oil was isolated in 76% yield, 0.3 g. $[\alpha]_D = +10.0^\circ$ (c=0.85, MeOH). MS(CI) m/e 388(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.8-1.05(m,12H), 1.2-1.4(m,8H), 1.45-1.72(m,4H), 2.06(m,1H), 3.1(m,1H), 3.2-3.5(m,2H), 3.5-3.65(m,1H), 4.92(dd,J=2,6Hz,1H), 6.6(d,J=15Hz,1H), 7.28(d,J=9Hz,1H), 7.3(m,1H), 7.6(d,J=15Hz,1H), 7.8(d,J=9Hz,1H), 8.58(d,J=6Hz,1H), 8.74(d,J=2Hz,1H). C,H,N analysis calculated for $C_{23}H_{37}N_3O_2$, 0.75 H_2O: C 68.88, H 9.68, N 10.48; found: C 68.74, H 9.31, N 10.21.

Example 19

N-(1',2',(3'S),4'-Tetrahydrocarbolinyl-3'-carbonyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 250 mg of the hydrochloride salt of example 2, N-L-1,2,3,4-tetrahydroharman-3-carboxylic acid (270 mg), EDCI (160 mg), HOBt (235 mg), and NMM (190 mL). The oily product was isolated in 38% yield (148 mg). $[\alpha]_D = -5.5^\circ$ (c=0.2, MeOH). MS(CI) m/e 455(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.8-1.0(m,12H), 1.2-

1.35(m,8H), 1.5(m,4H), 1.6(m,1H), 2.05(m,1H), 2.55-2.82(m,1H), 3.1-3.4(m,4H), 3.55(m,2H), 4.1(m,1H), 4.75(m,1H), 7.0-7.15(m,2H), 7.25(d,J=9Hz,1H), 7.45(d,J=9Hz,1H), 7.8(bs,1H), 7.85(bs,1H), 8.26(s,1H). C,H,N analysis calculated for $C_{27}H_{42}N_4O_2$, 0.75 H_2O: C 69.27, H 9.36, N 11.97; found: C 69.58, H 9.16, N 11.91.

Example 20

N-(1'-Hydroxy-2'-naphthoyl)-R-Valine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 250 mg of the hydrochloride salt of example 2, 1-hydroxy-2-naphthoic acid (160 mg), EDCI (180 mg), HOBt (240 mg), and NMM (200 µL). Product was isolated in 85% yield (310 mg). mp= 85-86°C. $[\alpha]_D$= +90.5° (c=0.6, MeOH). MS(CI) m/e 427(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.05(m,6H), 1.25-1.4(m,8H), 1.5-1.7(m,4H), 2.15(m,1H), 3.05(m,1H), 3.25(m,1H), 3.5(m,1H), 3.65(m,1H), 5.06(dd,J=3,9Hz,1H), 7.2(d,J=9Hz,1H), 7.35(d,J=10Hz,1H), 7.45(d,J=10Hz,1H), 7.5(dd,J=3,6Hz,1H), 7.6(dd,J=3,6Hz,1H), 7.75(d,J=7Hz,1H), 8.4(d,J=9Hz,1H), 10.6(bs,1H). C,H,N analysis calculated for $C_{26}H_{38}N_2O_3$: C 73.20, H 8.98, N 6.57; found: C 73.24, H 9.02, N 6.55.

Example 21

N-(t-Butyloxycarbonyl)-R-Norleucine-di-n-pentylamide

N-(t-Butyloxycarbonyl)-R-Norleucine (1.2 g, 5.2 mmol) was stirred at 0°C in 40 mL of CH_2Cl_2 with BOPCl (1.5 g, 5.9 mmol), and TEA (0.7 mL, 5.2 mmol). To this reaction mixture was added di-n-pentylamine (2.5 mL, 10.5 mmol).

The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl, saturated $NaHCO_3$ solution, water and then the organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was chromatographed using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 75% yield (1.45 g). MS(CI) m/e 371(m+H)$^+$, ^{1}H NMR($CDCl_3$,300MHz) δ 0.9-1.2(m,9H), 1.24-1.35(m,12H), 1.5(s,9H), 1.55-1.6(m,4H), 1.88(m,2H), 3.1(m,1H), 3.32(m,1H), 3.42(m,1H), 3.6(m,1H), 5.15(m,1H), 6.9(d,J=10Hz,1H).

Example 22

R-Norleucine-di-n-pentylamide hydrochloride

The product of example 21 (1.4g, 3.8 mmol) was dissolved in 4 N HCl in dioxane (25 mL) and stirred at room temperature for an hour. When the reaction was complete by tlc the solvents were evaporated in vacuo and hexane and diethylether were added. The residue was triturated with these solvents and the solid product was filtered away in quantitative yield. $[\alpha]_D = -1.4^\circ$ (c=0.6, MeOH). MS(CI) m/e 271(m+H)$^+$. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.87(m,9H), 1.2-1.4(m,12H), 1.42-1.6(m,4H), 1.7(m,2H), 3.0(m,1H), 3.1-3.3(m,2H), 3.53(m,1H), 4.14(bs,1H), 8.25(bs,2H).

Example 23

N-(3'-Quinolylcarbonyl)-R-Norleucine-di-n-pentylamide

The hydrochloride of example 22 (240 mg, 0.87 mmol), EDCI (170 mg), HOBt (240 mg) and quinoline-3-carboxylic acid (150 mg) were stirred at 0°C under nitrogen in 20 mL anhydrous CH_2Cl_2. To this mixture was added 200 µL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethylacetate and water and the organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using ethylacetate and hexane as the elutant mixture to provide 200 mg of the glassy product (54% yield) after evaporation of the volatiles. $[\alpha]_D = -10.5^\circ$ (c=1.0, MeOH). MS(CI) m/e 426(m+H)$^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,9H), 1.35(m,12H), 1.55(m,2H), 1.65-1.80(m,4H), 3.10(m,1H), 3.25-3.35(m,1H), 3.4(m,1H), 3.55-3.6(m,1H), 5.15(m,1H), 7.4(d,J=9Hz,1H), 7.6(dd,J=3,7Hz,1H), 7.8(dd,J=3,7Hz,1H), 7.9(d,J=9Hz,1H), 8.15(d,J=9Hz,1H), 8.6(d,J=2Hz,1H), 9.35(d,J=3Hz,1H). C,H,N analysis calculated for $C_{26}H_{39}N_3O_2$, 0.3 EtOAc: C 72.27, H 9.23, N 9.27; found: C 72.26, H 9.01, N 9.54.

Example 24

N-(2'-Indolylcarbonyl)-R-Norleucine-di-n-pentylamide

The hydrochloride salt of example 22 (0.30 g, 1.0 mmol) was stirred in 10 mL of CH_2Cl_2 with NMM (0.2 mL, 2.0 mmol) under nitrogen at 0°C. EDCI (0.2 g, 1.1 mmol) and HOBt (0.27 g, 2.0 mmol) were added followed by the

addition of indole-2-carboxylic acid (0.162 g, 1.0 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The product was crystallized from ethylacetate and hexane to provide a glass 0.285 g (69%). $[\alpha]_D = -10.6^o$ (c=0.8, MeOH). MS(CI) m/e 414(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,9H), 1.2-1.4(m,10H), 1.5-1.7(m,6H), 1.86(m,2H), 3.15(m,1H), 3.3-3.4(m,2H), 3.58(m,1H), 5.1(m,1H), 7.0(d,J=2Hz,1H), 7.15(dd,J=3,7Hz,1H), 7.3(m,2H), 7.4(d,J=9Hz,1H), 7.67(d,J=9Hz,1H), 9.4(s,1H). C,H,N analysis calculated for $C_{25}H_{39}N_3O_2$, 0.75 H_2O: C 70.30, H 9.55, N 9.84; found: C 70.38, H 9.20, N 9.85.

Example 25

N-(t-Butyloxycarbonyl)-R-(O-benzyl)Serine-di-n-pentylamide

N-(t-Butyloxycarbonyl)-R-(O-benzyl)serine (3.0 g, 10.15 mmol) was stirred at 0°C in 50 mL of CH_2Cl_2 with BOPCl (2.8 g, 11 mmol) and 2.0 mL (1.5 mmol) of TEA. To this reaction mixture was added di-n-pentylamine (7 mL, 35 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an

additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl solution, saturated $NaHCO_3$, water and then the organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the elutant system in the ratio (1:4). The product was isolated as an oil in 44% yield (1.9 g). MS(CI) m/e 435(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.89(m,6H), 1.28(m,8H), 1.4(s,9H), 1.55(m,4H), 3.05-3.2(m,2H), 3.4-3.65(m,4H), 4.5(m,2H), 4.85(m,1H), 5.35(d,J=7Hz,1H), 7.31(m,5H).

Example 26

R-(O-Benzyl)Serine-di-n-pentylamide hydrochloride

The product of example 25 (0.43 g, 1.0 mmol) was dissolved in 4 N HCl in dioxane (10 mL) and stirred under inert atmosphere (N_2) for an hour. When the reaction was complete by tlc the solvents were evaporated in vacuo and hexane and diethylether were added. The residue was triturated with these two solvents and the solvents again removed in vacuo. This procedure was repeated several times until the product was obtained as a glassy solid in 93% yield (0.35 g). $[\alpha]_D$= +1.6^o (c=0.5, MeOH). MS(CI) m/e 335(m+H)$^+$.

Example 27

N-(3'-Quinolylcarbonyl-R-(O-benzyl)Serine-di-n-pentylamide

The hydrochloride salt of example 26 (0.35 g, 0.95 mmol) was stirred in 25 mL of CH_2Cl_2 with NMM, (0.22 mL, 2 mmol) under N_2 at 0^oC. EDCI (0.19 g, 1.0 mmol) and HOBt (0.27, 2 mmol) were added followed by the addition of quinoline-3-carboxylic acid (0.165 g, 0.95 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The product was crystallized from ethylacetate and hexane to provide a semisolid, 0.44 g (94%). $[\alpha]_D = -4.0^o$ (c=0.45, MeOH). MS(CI) m/e 490(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.2-1.4(m,8H), 1.5-1.6(m,4H), 3.05-3.28(m,2H), 3.5-3.7(m,2H), 3.8(m,2H), 4.57(m,2H), 5.4(m,1H), 7.3(m,5H), 7.4(d,J=9Hz,1H), 7.62(dd,J=2,7Hz,1H), 7.81(dd,J=2,7Hz,1H), 7.9(d,J=8Hz,1H), 8.15(d,J=9Hz,1H), 8.58(d,J=3Hz,1H), 9.3(d,J=3Hz,1H). C,H,N analysis calculated for $C_{30}H_{39}N_3O_3$, 0.75 H_2O: C 71.61, H 8.11, N 8.35; found: C 71.73, H 8.01, N 8.21.

Example 28

N-(t-Butyloxycarbonyl)-R-Phenylalanine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 2 utilizing N-(t-Butyloxycarbonyl)-R-Phenylalanine (0.8 g, 3.1 mmol), BOPCl (1.2, 4.06 mmol), dipentylamine (3.1 mL, 15 mmol), and TEA (0.4 mL, 3.1 mmol). The oily product was isolated in 65.5% yield (0.87 g). $[\alpha]_D = +7.0^o$ (c=1.0, MeOH). MS(CI) m/e 405(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.15-1.45(m,8H), 1.5(s,9H), 1.55-1.6(m,4H), 2.9-3.1(m,5H), 3.5(m,1H), 4.25(m,1H), 5.3(d,J=9Hz,1H), 7.25(m,5H).

Example 29

N-(t-Butyloxycarbonyl)-(2R,3S)-(O-benzyl)Threonine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 1 utilizing N-(t-Butyloxycarbonyl)-D-(O-benzyl)- threonine (5 g, 16.2 mmol), BOPCl (8.2 g, 16.2 mmol), dipentylamine (16 mL, 78.5 mmol), and TEA (2.1 mL, 16.2 mmol). The product was isolated in 58% yield (4.15 g). MS(CI) 449(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(t,J=6Hz,6H), 1.18(d,J=6Hz,3H), 1.2-1.35(m,8H), 1.45(s,9H), 1.5-1.6(m,4H), 3.0-3.18(m,2H), 3.41-3.63(m,2H), 3.75(m,1H), 4.57(dd,J=12,18Hz,2H), 4.65(m,1H), 5.5(d,J=9Hz,1H), 7.30(m,5H).

Example 30

(2R,3S)-(O-Benzyl)Threonine-di-n-pentylamide hydrochloride

The product of example 29 (1 g, 2.22 mmol) was deprotected and isolated in a similar manner to that in example 2. The product was isolated as an oil. $[\alpha]_D$ = +13.3° (c=1.1, MeOH). MS(CI) m/e 359(m+H)$^+$. ^1H NMR(DMSO$_{d6}$,300MHz) δ 0.86(m,6H), 1.08-1.32(m,11H), 1.48(m,4H), 3.03(m,2H), 3.42(m,2H), 3.88(m,1H), 4.2(d,J=6Hz,1H), 4.56(m,2H), 7.35(m,5H), 8.35(bs,2H).

Example 31

N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-benzyl)Threonine-di-n-pentylamide

The hydrochloride salt of example 30 (0.25 g, 0.65 mmol) was stirred in 15 mL of CH_2Cl_2 with NMM (0.175 mL, 1.3 mmol) under nitrogen at 0°C. EDCI (0.15 g, 0.8 mmol) and HOBt (0.18 g, 1.3 mmol) were added followed by the addition of quinoline-3-carboxylic acid (0.115 g, 0.65 mmol). The reaction mixture was stirred overnight (warming to ambient temperature). The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The oily product was isolated in 62% yield (0.2g). $[\alpha]_D$= -4.1°

(c=1.0, MeOH). MS(CI) m/e 504(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.2-1.45(m,11H), 1.5-1.7(m,4H), 3.0-3.25(m,2H), 3.56-3.7(m,2H), 3.9(m,1H), 4.5(m,2H), 5.3(apparent q,J=4.5Hz,1H), 7.2-7.3(m,5H), 7.56(d,J=6Hz,1H), 7.65(t,J=7Hz,1H), 7.8(t,J=7Hz,1H), 7.92(d,J=9Hz,1H) 8.15(d,J=9Hz,1H), 8.63(d,J=2Hz,1H), 9.35(d,J=3Hz,1H). C,H,N analysis calculated for $C_{31}H_{41}N_3O_3$, 1.6 H_2O: C 69.92, H 7.89, N 8.37; found: C 69.81, H 7.78, N 8.08.

Example 32

N-(3'-Quinolylcarbonyl)-(2R,3S)-Threonine-di-n-pentylamide

The product of example 31 (1 g, 2 mmol) was stirred in 20 mL of CH_2Cl_2 and 7 mL of borontristrifluoroacetate (1.0 M solution in trifluoroacetic acid) was added at 0°C. The mixture was stirred approximately 1 hour The tlc revealed some starting material therefore another 5 mL of borontristrifluoroacetate and 5 mL trifluoroacetic acid were added. The reaction proceeded overnight to completion by tlc analysis. The reaction mixture was diluted with MeOH and then concentrated in vacuo. The residue was purified by chromatography using ethylacetate and hexane as the elutant mixture. The pure fractions were pooled together and the desired product characterized as the di-trifluoroacetic acid salt. mp= 84-6°C. $[\alpha]_D$= -11.6° (c=0.55, MeOH). MS(CI) m/e 414(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.13(d,J=7Hz,3H), 1.15-1.38(m,8H), 1.48(m,2H), 1.6(m,2H), 3.1(m,1H), 3.32-3.53(m,4H), 4.05(m,1H), 4.9(t,J=6Hz,1H), 7.7(t,J=6Hz,1H),

7.88(t,J=7Hz,1H), 8.1(d,J=9Hz,1H), 8.8(d,J=9Hz,1H), 8.93(bs,1H), 9.31(bs,1H), 10.02(bs,1H). C,H,N analysis calculated for $C_{24}H_{35}N_3O_3$, 2 CF_3CO_2H: C 52.42, H 5.81, N 6.55; found: C 52.31, H 5.62, N 6.66.

Example 33

N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-acetyl)Threonine-di-n-pentylamide

Pyridine (20 µL) and acetic anhydride (60 µL) were added to the product of example 32 (51 mg, 0.125 mmol) which was dissolved in acetonitrile (2 mL). The reaction mixture was stirred overnight at room temperature. Ethylacetate was added and this solution was washed successively with water and brine. The organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate and hexane as the elutant system in the ratio (4:1). The product was isolated as a glass in 44% yield (25 mg). MS(CI) m/e 456(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.25-1.45(m,11H), 1.52(m,2H), 1.7(m,2H), 2.05(s,3H), 3.1(m,2H), 3.3-3.6 (m,3H), 5.28(m,1H), 5.44(m,1H), 7.35(d,J=9Hz,1H), 7.65(t,J=7Hz,1H), 7.82(t,J=7Hz,1H), 7.95(d,J=7Hz,1H), 8.18(d,J=9Hz,1H), 8.6(d,J=3Hz,1H), 9.35(d,J=3Hz,1H). C,H,N analysis calculated for $C_{26}H_{37}N_3O_4$, 0.4 H_2O: C 67.48, H 8.23, N 9.08; found: C 67.69, H 8.20, N 8.60.

Example 34

N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-methyl)Threonine-di-n-pentylamide

Lithium bis(trimethylsilyl)amide in THF (0.15 mL of 1.0 M solution in THF) was added to a cooled (-10^{o}C) solution of the product of example 32 (55 mg, 0.14 mmol) in 2 mL tetrahydrofuran (THF) and then methyl iodide (0.015 mL) was added. The reaction mixture was stirred approximately 1 hour and slowly warmed to room temperature. Tlc revealed some starting material therefore another equivalent of methyl iodide (0.01 mL) was added. The reaction then proceeded to completion by tlc. The reaction mixture was concentrated in vacuo. Ethylacetate was added to the residue, which was then washed with water and brine. The ethylacetate extract was dried over $MgSO_4$. Filtration and concentration of the filtrate in vacuo, provided a residue which was purified by chromatography using ethylacetate and hexane as the elutant mixture. An oil was isolated in 47% yield (28 mg). MS(CI) m/e 428(m+H)$^{+}$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.92(m,6H), 1.25(d,J=6Hz,3H), 1.25-1.4(m,8H), 1.55-1.6(m,4H), 3.05(m,1H), 3.2-3.3(m,2H), 3.35(s,3H), 3.58-3.82(m,2H), 5.25(m,1H), 7.45(d,J=9Hz,1H), 7.65(t,J=6Hz,1H), 7.8(t,J=6Hz,1H), 7.9(d,J=9Hz,1H), 8.18(d,J=9Hz,1H), 8.6(d,J=3Hz,1H), 9.35(d,J=3Hz,1H).

Example 35

N-(t-Butyloxycarbonyl)-3-(2'-thienyl)-R-Alanine-di-n-pentylamide

N-(t-Butyloxycarbonyl)-R-3-(2'-thienyl)-Alanine (0.78 g, 3.25 mmol) was stirred at $0^{o}C$ in 25 mL of CH_2Cl_2 with BOPCl (0.44 g, 3.25 mmol) and 0.5 mL, (3.25 mmol) of TEA. To this reaction mixture was added di-n-pentylamine (2 mL, 10 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reactions stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl solution, saturated $NaHCO_3$ solution, water and then the organic solution was dried over magnesium sulfate. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 57% yield (0.76 g). $[\alpha]_D = -2.27^{o}$ (c=0.66, MeOH). MS(CI) m/e 411$(m+H)^+$, 355, 311. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.15-1.38(m,10H), 1.45(s,9H), 1.51(m,2H), 3.1(m,4H), 3.22(m,1H), 3.4(m,1H), 4.75(apparent q,J=10Hz,1H), 5.45(d,J=9Hz,1H), 6.83(d,J=6Hz,1H), 6.9(t,J=4Hz,1H), 7.15(d,J=6Hz,1H).

Example 36

R-3-(2'-Thienyl)-Alanine-di-n-pentylamide hydrochloride

The product of example 35 (0.22 g, 0.54 mmol) was deprotected and isolated in the same manner as that in example 2 in quantitative yield. MS(CI) m/e 327$(M+H)^+$.

Example 37

N-(3'-Quinolylcarbonyl)-3-(2'-thienyl)-R-Alanine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing (80 mg, 0.23 mmol) of the hydrochloride salt of example 36, quinoline-3-carboxylic acid (40 mg), EDCI (50 mg), HOBt (62 mg), and NMM (51 µL). An oil was isolated in 45% yield, (48 mg). MS(CI) m/e 466$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.2-1.4(m,8H), 1.45-1.65(m,4H), 3.05-3.4(m,4H), 3.45-3.6(m,2H), 5.35(dd,J=6,7Hz,1H), 6.87(d,J=3Hz,1H), 6.94(m,1H), 7.18(d,J=6Hz,1H), 7.4(d,J=9Hz,1H), 7.63(dd,J=3,7Hz,1H), 7.8(dd,J=3,7Hz,1H), 7.9(d,J=8Hz,1H), 8.15(d,J=8Hz,1H), 8.6(d,J=3Hz,1H), 9.32(d,J=3Hz,1H). C,H,N analysis calculated for $C_{27}H_{35}N_3O_2S$, 0.9 H_2O: C 67.29, H 7.70, N 8.72; found: C 67.60, H 7.47, N 8.98.

Example 38

N-(t-Butyloxycarbonyl)-S-Valine-di-n-pentylamide

The reaction and product isolation were performed in a similar manner to that in example 1 utilizing N-(t-Butyloxycarbonyl)- S-Valine (2.5 g, 11.5 mmol), BOPCl (3.5 g, 13.8 mmol) and dipentylamine (11.6 mL, 58 mmol), and

TEA (1.6 mL, 12 mmol). The oily product was isolated in 55% yield (2.25 g). $[\alpha]_D = -21.1^{\circ}$ (c=1.0, MeOH). MS(CI) m/e 357(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.05(m,6H), 1.25-1.35(m,8H), 1.45(s,9H), 1.5-1.55(m,4H), 1.95(m,1H), 3.0(m,1H), 3.2(m,1H), 3.36(m,1H), 3.6(m,1H), 4.4(dt,J=3,7Hz,1H), 5.24(d,J=9Hz,1H).

Example 39

S-Valine-di-n-pentylamide hydrochloride

The product of example 38 (0.2 g, 0.57 mmol) was deprotected and the product isolated as in example 2 in quantitative yield. MS(CI) m/e 257(m+H)$^+$.

Example 40

N-(3'-Quinolylcarbonyl)-S-Valine-di-n-pentylamide

The reaction sequence was performed in a similar manner to that in example 3 utilizing 175 mg of the hydrochloride salt of example 39, quinoline-3-carboxylic acid (110 mg), EDCI (125 mg), HOBt (165 mg), and NMM (75 µL). The glassy product was isolated in 80% yield, (198 mg). $[\alpha]_D = +12.95^{\circ}$ (c=0.8, MeOH). MS(CI) m/e 412(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.8-1.05(m,12H), 1.2-1.44(m,8H), 1.55(m,4H), 2.15(m,1H), 3.1(m,1H), 3.3(m,1H), 3.5(m,1H), 3.65(m,1H), 5.1(dd,J=3,6Hz,1H), 7.25(d,J=7Hz,1H), 7.62(t,J=7Hz,1H), 7.8(t,J=7Hz,1H), 7.9(d,J=8Hz,1H), 8.15(d,J=9Hz,1H), 8.61(d,J=3Hz,1H), 9.35(d,J=3Hz,1H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_2$, 0.25 H_2O: C 72.16, H 9.09, N 10.10; found: C 72.41, H 9.21, N 9.97.

Example 51

N-(t-Butyloxycarbonyl)-(N^{im}-tosyl)-R-Histidine-di-n-pentylamide

N-(t-Butyloxycarbonyl)-R-(N^{im}-tosyl)-histidine, (4.95 g, 12.6 mmol) was stirred at 0°C in 50 mL of CH_2Cl_2 with BOPCl (3.2 g, 12.6 mmol) and 1.65 mL (12.6 mmol) TEA. To this reaction mixture was added di-n-pentylamine (7.7 mL, 38 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue was taken up in ethylacetate and washed with water, 1 N HCl solution, saturation $NaHCO_3$, water. The organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 75% yield (5.1 g). $[\alpha]_D = +8.8°$ (c=1.0, MeOH). MS(CI) m/e 549(m+H)$^+$. ^1H NMR($DMSO_{d6}$,300MHz) δ 0.85(m,6H), 1.05-1.46(m,21H), 2.42(s,3H), 2.67(m,2H), 3.03-3.15(m,4H), 4.52(m,1H), 7.0(s,1H), 7.28(d,J=7Hz,1H), 7.49(d,J=7Hz,2H), 7.9(d,J=7Hz,2H), 8.28(s,1H). C,H,N analysis calculated for $C_{28}H_{44}N_4O_5S$: C 61.28, H 8.08, N 10.21; found: C 61.04, H 8.05, N 10.10.

Example 42

$(N^{im}$-Tosyl)-R-Histidine-di-n-pentylamide

To a solution of the product of example 41 (6.7 g, 12.21 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (TFA, 40-50 mL). The reaction mixture was stirred at room temperature 60 minutes. When reaction was complete by tlc, the solvents were evaporated several times in vacuo and CH_2Cl_2 was added with a saturated solution of $NaHCO_3$. The reaction mixture was stirred vigorously another 1 hr and after separation of layers, the organic layer was washed several times with water and brine. The CH_2Cl_2 layers and washings were dried over magnesium sulfate. The product was then concentrated in vacuo. The semisolid product was isolated and dried in a vacuum oven over P_2O_5 at room temperature, 5.1 g (93% yield). $[\alpha]_D = -9.4^o$ (c=1.0, MeOH). MS(CI) m/e 449$(m+H)^+$, 264, 295. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.1-1.35(m,8H), 1.47-1.6(m,4H), 2.45(s,3H), 2.9-3.2(m,6H), 3.4-3.55(m,2H), 4.5(m,1H), 7.18(s,1H), 7.35(d,J=8Hz,2H), 7.82(d,J=8Hz,2H), 7.95(s,1H).

Example 43

N-(2'-Indolylcarbonyl)-R-Histidine-di-n-pentylamide

The compound of example 42 (170 mg, 0.5 mmol), EDCI (105 mg), HOBt (135 mg) and indole-2-carboxylic acid (85 mg) were stirred at 0°C under nitrogen in 10 mL of anhydrous CH_2Cl_2. To this mixture was added 110 µL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into

ethylacetate and water and the organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using chloroform/methanol/ammonia as the elutant mixture to provide 98 mg of the semisolid product (45% yield) after evaporation of the volatiles. $[\alpha]_D = +9.8^o$ (c=0.46, MeOH). MS(CI) m/e 438(m+H)$^+$, 253, 281. ^1H NMR($CDCl_3$,300MHz) δ 0.75-0.95(m,6H), 1.2(m,8H), 1.5(m,4H), 3.13(m,4H), 3.3(m,1H), 3.4(m,1H), 3.5(m,2H), 5.32(m,1H), 6.8(s,1H), 6.9(s,1H), 7.1(t,J=7Hz,2H), 7.2(t,J=7Hz,2H), 7.35(d,J=9Hz,1H), 7.59(d,J=9Hz,1H), 9.8(s,1H). C,H,N analysis calculated for $C_{25}H_{35}N_5O_2$, 0.5 H_2O: C 67.23, H 8.13, N 15.68; found: C 67.24 H 8.06, N 15.24.

Example 44

N^α-(t-Butyloxycarbonyl)-N^ε-(benzyloxycarbonyl)-R-Lysine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 1 utilizing N^α-t-Butyloxycarbonyl-R-(N^ε-benzyloxycarbonyl)Lysine (5 g, 13.15 mmol), BOPCl (6.7 g, 26.3 mmol), di-n-pentylamine (26 mL, 131 mmol) and TEA (1.8 mL, 13.5 mmol) in CH_2Cl_2 (25 mL). The oily product was isolated in 64.5% yield (4.4 g). $[\alpha]_D = +65.3^o$ (c=0.15, MeOH). MS(CI) m/e 520(m+H)$^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.2-1.35(m,12H), 1.41(s,9H), 1.5-1.66(m,4H), 3.05-3.25(m,4H), 3.3(m,2H), 3.5(m,2H), 4.53(m,1H), 4.9(m,1H), 5.1(s,2H), 5.38(d,J=9Hz,1H), 7.3(m,5H).

Example 45

N-(t-Butyloxycarbonyl)-3-(1'-naphthyl)-R-Alanine-di-n-pentylamine

N-(t-Butyloxycarbonyl)-3-(1'-naphthyl)-R-Alanine (0.35 g, 1.1 mmol) was stirred at $0^{o}C$ in 25 mL of CH_2Cl_2 with BOPCl, (0.3 g, 1.2 mmol), and 0.15 mL of TEA (1.2 mmol). To this reaction mixture was added di-n-pentylamine (0.8 mL, 4 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl solution, saturated $NaHCO_3$, water and then the organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 65% yield (0.25 g). MS(CI) m/e 455(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.7-0.8(m,6H), 0.9(m,8H), 1.2-1.3(s,4H), 1.35(s,9H), 3.0(m,2H), 3.35(m,2H), 3.5-3.6(m,2H), 4.3(m,1H), 7.4(m,1H), 7.45-7.55(m,2H), 7.6(m,1H), 7.8 (d,J=9Hz,1H), 7.85(d,J=9Hz,1H), 8.35(d,J=9Hz,1H), 8.9(bs,1H).

Example 46

3-(1'-Naphthyl)-R-Alanine-di-n-pentylamide hydrochloride

The product of example 45 (0.32 g, 0.72 mmol) was dissolved in 4 N HCl in dioxane (10 mL) and stirred under

inert atmosphere (N_2) for an hour. When the reaction was complete by tlc the solvents were evaporated in vacuo and hexane and diethylether added. The residue was triturated with these two solvents until the product was obtained as a glassy solid in quantitative yield.
MS(CI) m/e 391(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz): δ 0.63(m,3H), 0.85(m,3H), 1.05-1.45(m,10H), 1.5-1.72(m,2H), 2.62(m,1H), 2.85(m,1H), 3.6-3.92(m,4H), 4.85(m,1H), 4.73(m,2H), 7.36(m,1H), 7.5(m,1H), 7.7(d,J=6Hz,1H), 7.75(d,J=6Hz,1H), 8.35(d,J=8Hz,1H), 8.92(bs,2H), 9.4(s,1H).

Example 47

N-(3'-Quinolylcarbonyl)-3-(1'-Naphthyl)-R-Alanine-di-n-pentylamide

The hydrochloride of example 46 (200 mg, 0.52 mmol), EDCI, HOBt (70 mg) and quinoline-3-carboxylic acid (90 mg) were stirred at 0°C under N_2 in 5 mL of anhydrous CH_2Cl_2. To this mixture was added 10µL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethylacetate and water and then the separated organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using ethylacetate and hexane as the elutant mixture to provide 180 mg of the oily product (68% yield) after removal of the volatiles.
MS(CI) m/e 510(m+H)$^+$, 280. ^{1}H NMR($CDCl_3$,300MHz) δ 0.72(m,3H), 0.9(m,3H), 1.1-1.45(m,10H), 1.5.1-6(m,2H), 2.38-2.6(m,2H), 2.85(m,1H), 3.47(m,2H), 3.9(m,1H),

5.6(m,1H), 7.35(d,J=6Hz,2H), 7.52(t,J=7Hz,2H), 7.6-7.7(m,3H), 7.72-7.93(m,3H), 8.15(d,J=9Hz,1H) 8.55(d,J=9Hz,1H), 8.6(d,J=3Hz,1H), 9.4(d,J=3Hz,1H).

Example 48

N-(t-Butyloxycarbonyl)-3-(2'-naphthyl)-R-Alanine-di-n-pentylamide

N-(t-Butyloxycarbonyl)-3-(2'-naphthyl)-R-Alanine (0.31 g, 1.0 mmol) was stirred at $0^{o}C$ in 25 mL of CH_2Cl_2 with BOPCl, (0.38 g, 1.5 mmol) and 0.2 mL of TEA (1.5 mmol). To this reaction mixture was added di-n-pentylamine (0.7 mL, 3.5 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl solution, saturated $NaHCO_3$, and water. The organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 62% yield (0.28 g). MS(CI) m/e $455(m+H)^+$, 355.

Example 49

3-(2'-Naphthyl)-R-Alanine-di-n-pentylamide hydrochloride

The product of example 48 (0.28 g, 0.6 mmol) was dissolved in 4 N HCl in dioxane (10 mL) and stirred under N_2 for an hour. When the reaction was complete by tlc the

solvents were evaporated in vacuo and then hexane and diethylether were added. The residue was triturated with these two solvents until the product was obtained as a glassy solid in 93% yield. MS(CI) m/e 355(m+H)$^+$.

Example 50

N-(3'-Quinolylcarbonyl)-R-Histidine-di-n-pentylamide

The free base of example 42 (3.7 g, 9.26 mmol), EDCI, (1.7 g, 9 mmol), HOBt (3.65 g) and 1.5 g quinoline-3-carboxylic acid were stirred at 0°C in 50 mL of anhydrous dimethylformamide (DMF) and CH_2Cl_2 in 1:1 ratio. After reaction was complete by tlc, solvents were evaporated under vacuum and the residue dissolved in large excess of ethylacetate (300 mL). Water was added and the organic extract was washed with 10% citric acid solution, and saturated $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using chloroform-methanol and ammonium hydroxide as the elutant mixture to provide 1.98 g (68.3%) product. $[\alpha]_D = -6.4°$ (c=0.25, MeOH). MS(CI) m/e 450(m+H)$^+$, 156. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.29(m,8H), 1.45-1.6(m,4H), 3.08-3.2(m,3H), 3.23-3.4(m,2H), 3.5-3.6(m,1H), 5.3(apparent q,J=9Hz,1H), 6.85(s,1H), 7.6(m,3H), 7.(t,J=6H,1H), 7.88(d,J=8Hz,1H), 7.97(d,J=8Hz,1H), 8.15(d,J=8Hz,1H), 8.6(d,J=3Hz,1H), 9.3(d,J=3Hz,1H). N-(3'-Quinolylcarbonyl)-(N^{im}-tosyl)-R-histidine-di-n-pentylamide (0.2 g) also was isolated refer to example 51.

Example 51

N-3'-Quinolylcarbonyl-(N^{im}-tosyl)-R-Histidine-di-n-pentylamide

The title compound of example 51 was isolated as a side product in the procedure in example 50. $[\alpha]_D = +13.3°$ (c=1.05, MeOH). MS(CI) m/e 604(m+H)$^+$, 450. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.3(m,8H), 1.45-1.7(m,4H), 2.25(s,3H), 3.0-3.13(m,3H), 3.25(m,1H), 3.35(m,1H), 3.5(m,1H), 5.36(apparent q,J=6Hz,1H), 7.15(m,3H), 7.6(t,J=7Hz,2H), 7.7(d,J=9Hz,2H), 7.8-7.9(m,2H), 7.95(d,J=2Hz,1H), 8.13(d,J=7Hz,1H), 8.45(d,J=3Hz,1H), 9.18(d,J=3Hz,1H). C,H,N analysis calculated for $C_{33}H_{41}N_5O_4S$: C 65.64, H 6.85, N 11.60; found: C 65.58, H 6.84, N 11.50.

Example 52

N^{ε}-(Benzyloxycarbonyl)-R-Lysine-di-n-pentylamide hydrochloride

The compound was prepared in similar manner to example 2 via deprotection of the product of example 44 using 4 N HCl in dioxane. The product was isolated in quantitative yield. MS(CI) m/e 420(m+H)$^+$.

Example 53

N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(benzyloxycarbonyl)-R-Lysine di-n-pentylamide

The reaction was performed in the similar manner to that in example 3 utilizing 1.0 g of hydrochloride salt of example 52 quinoline-3-carboxylic acid (0.38 g), EDCI (0.45 g), HOBT (0.6 g), and NMM (0.48 mL). The oily

product was isolated in 72% yield. $[\alpha]_D = +2.7^o$ (c=0.7, MeOH). MS(CI) m/e 575(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.3-1.62(m,8H), 1.53(m,6H), 1.65(m,2H), 1.85(m,2H), 3.05-3.55(m,1H), 5.05(m,1H), 5.15(m,2H), 7.28(m,5H), 7.55(t,J=8Hz,1H), 7.8(m,3H), 8.18(d,J=9Hz,1H), 8.58(d,J=2Hz,1H), 9.32(d,J=2Hz,1H). C,H,N calculated for $C_{34}H_{46}N_4O_4$: C 71.05, H 8.07, N 9.75; found: C 71.00, H 8.18, N 9.68.

Example 54

N-(3'-Quinolylcarbonyl)-R-Lysine-di-n-pentylamide

To a suspension of 0.5 g 10% Pd/C in methanol (MeOH, 25 mL) and cyclohexadiene (3 mL) under N_2 was added a solution of the product of example 53 (0.51 g, 0.89 mmol) in methanol via cannula. The reaction mixture was stirred overnight at ambient temperature. Cyclohexadiene (2 mL) was added and the reaction was continued overnight. The mixture was filtered through celite and washed several times with methanol. The filtrate and washings were combined and concentrated in vacuo. The residue was subjected to flash chromatography using chloroform-methanol and ammonium hydroxide 90:10:1 as the elutant mixture. Lyophilization provided product in 64% yield (0.25 g). MS(CI) m/e 441(m+H)$^+$. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.85(m,6H), 1.15-1.35(m,8H), 1.4-1.65(m,4H), 1.7(m,2H), 1.75(m,2H), 2.7(m,2H), 3.1-3.5(m,8H), 4.9(m,1H), 7.7(t,J=6Hz,1H), 7.88(t,J=6Hz,1H), 8.1(d,J=8Hz,2H), 8.9(d,J=3Hz,1H), 9.0(d,J=3Hz,1H), 9.3(d,J=3Hz,1H). C,H,N analysis calculated for $C_{26}H_{40}N_4O_2$, H_2O: C 69.45, H 8.97, N 12.46; found: C 69.48, H 8.76, N 12.03.

Example 55

N-(t-Butyloxycarbonyl)-R-(4'-Hydroxyphenyl)glycine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 1 utilizing N-(t-Butyloxycarbonyl)-R-4'-hydroxy phenylglycine (5 g, 18.7 mmol), BOPCl (5.1 g, 20 mmol), dipentylamine (8 mL, 37 mmol), and TEA (2.6 mL). The product was isolated in 78% yield (5.9 g). MS(CI) m/e 407(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.1-1.35(m,8H), 1.3(s,9H), 1.45-1.58(m,4H), 3.0(m,1H), 3.15(m,2H), 3.45(m,1H), 5.42(d,J=9Hz,1H), 6.02(d,J=9Hz,1H), 6.5(s,1H), 6.75(d,J=9Hz,2H), 7.18(d,J=9Hz,2H).

Example 56

N-(8'-Hydroxy-2'-quinolylcarbonyl)-R-Valine-di-n-pentylamide

The title compound was prepared in a similar fashion to that in example 3. mp= 143-4^{o}C. MS(CI) m/e 428(m+H)$^+$, 243, 158. ^{1}H NMR($CDCl_3$,300MHz) δ 8.58(d,J=10Hz,1H), 8.31(s,2H), 8.09(s,1H), 7.54(m,1H), 7.39(dd,J=1,8Hz,1H), 7.24(m,1H), 5.01(dd,J=7,10Hz,1H), 3.65(dt,J=7,16Hz,1H), 3.28-3.55(m,2H), 3.06(dt,J=7,14Hz,1H), 2.22(septet,J=7Hz,1H), 1.50-1.75(m,4H), 1.25-1.42(m,8H), 1.06(d,J=7Hz,3H), 1.03(d,J=7Hz,3H), 0.92(t,J=7Hz,3H), 0.89(t,J=7Hz,3H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_3$, 0.1 H_2O: C 69.93, H 8.73, N 9.79; found: C 69.78, H 8.51, N 9.61.

Example 57

R-Phenylalanine-di-n-pentylamide hydrochloride

The compound was prepared in similar manner to example 2 via deprotection of N-t-Butyloxycarbonyl-R-Phenylalanine- di-n-pentylamide, the product of example 28, using 4 N HCl in dioxane. The product was isolated in quantitative yield. MS(CI) m/e 305$(m+H)^+$.

Example 58

N-(3'-Quinolylcarbonyl)-R-Phenylalanine-di-n-pentylamide

The hydrochloride of example 57 (870 mg, 2.46 mmol), EDCI (550 mg), HOBt (300 mg), and quinoline-3-carboxylic acid (430 mg) were stirred at 0^oC under N_2 in 25 mL of anhydrous CH_2Cl_2. To this mixture was added 550 µL of NMM and the mixture was stirred overnight (warming to ambient temperature). The reaction mixture was poured into ethylacetate and water and the organic solution was separated. The organic extract was washed successively with water, 10% citric acid solution, and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography using ethylacetate and hexane as the elutant mixture to yield 870 mg of product (77%) after removal of the volatiles. $[\alpha]_D = +12.9^o$ (c=1.05, MeOH). MS(CI) m/e 460$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.15-1.4(m,8H), 1.5-1.55(m,4H), 2.9-3.12(m,3H), 3.2(m,2H), 3.48-3.6(m,1H), 5.35(m,1H), 7.27(m,5H), 7.48(d,J=10Hz,1H), 7.62(t,J=8Hz,1H), 7.8(t,J=8Hz,1H), 7.9(d,J=9Hz,1H), 8.15(d,J=9Hz,1H), 8.55(d,J=3Hz,1H), 9.38(d,J=3Hz,1H).

C,H,N analysis calculated for $C_{29}H_{37}N_3O_2$, 0.5 H_2O: C 74.32, H 8.39, N 8.97; found: C 73.92, H 8.05, N 8.83.

Example 59

N-(2'-Methylphenylaminocarbonyl)-R-Valine-di-n-pentylamide

A solution of hydrochloride of example 2 (0.15 g, 0.52 mmol), 2-methyl-phenylisocyanate (0.1 g) and triethylamine (0.1 mL) was allowed to react at ambient temperature. The solvent was removed in vacuo and the residue dissolved in ethylacetate. Water was added and the mixture extracted several times with EtOAc. The combined ethylacetate extracts were washed with brine and dried over $MgSO_4$. The volatiles were removed in vacuo and the residue purified by chromatography. The oily product was isolated in 80% yield. $[\alpha]_D = +1.5^o$ (c=0.4, MeOH). MS(CI) m/e 390(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.8-1.0(m,12H), 1.12-1.41(m,8H), 1.42-1.78(m,4H), 2.01(m,1H), 2.22(s,3H), 3.25(m,1H), 3.35(m,2H), 3.51(m,1H), 4.7(m,1H), 6.5(m,1H), 6.7(s,1H), 7.04(t,J=6Hz,1H), 7.16(m,2H), 7.53(d,J=9Hz,1H). C,H,N analysis calculated for $C_{23}H_{39}N_3O_2$: C 70.91, H 10.09, N 10.79; found: C 70.57, H 9.46, N 10.57.

Example 60

N^{α}-(t-Butyloxycarbonyl)-N^{ε}(2'-chlorobenzyloxycarbonyl)-R-Lysine-di-n-pentylamide

N^{α}-(t-Butyloxycarbonyl)-N^{ε}-(2'-chlorobenzyloxycarbonyl)-R-Lysine (1.0 g, 2.4 mmol) was stirred at 0°C in 25 mL of CH_2Cl_2 with BOPCl, (0.65 g, 2.6

mmol), and TEA (0.35 mL, 2.4 mmol). To this reaction mixture was added di-n-pentylamine (2.5 mL, 12 mmol). The mixture was stirred overnight and allowed to warm to room temperature. An additional equivalent of BOPCl was added after 18 hrs and the reaction stirred an additional day at ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed with water, 1 N HCl solution, saturated $NaHCO_3$, and water. The organic solution was dried over $MgSO_4$. After filtration and concentration of the filtrate in vacuo, the residue was purified by chromatography using ethylacetate-hexane as the solvent system in the ratio (1:4). The product was isolated as an oil in 53% yield (0.7 g). MS(CI) m/e 554(m+H)$^+$, 326. ^{1}H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.2-1.38(m,12H), 1.42(s,9H), 1.5-1.7(m,4H), 3.02-3.45(m,4H), 3.48(m,4H), 4.5(m,1H), 5.01(m,1H), 5.2(s,2H), 5.4(d,J=9Hz,1H), 7.25(m,2H), 7.3-7.45(m,2H).

Example 61

N^{ε}-(2'-Chlorobenzyloxycarbonyl)-R-Lysine-di-n-pentylamide hydrochloride

The compound was prepared in similar manner to example 2 via deprotection of the product of example 60, using 4 N HCl in dioxane. The product was isolated in quantitative yield. MS(CI) m/e 454(m+H)$^+$, free base.

Example 62

N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(2'-chlorobenzyloxycarbonyl)-R-Lysine-di-n-pentylamide

The hydrochloride salt of example 61 (0.5 g, 1.02 mmol) was stirred in 15 mL of CH_2Cl_2 with NMM (0.24 mL, 2.2 mmol) under N_2 at 0°C. EDCI (0.25 g, 1.3 mmol) and HOBt (0.3 g, 2.2 mmol) were added followed by the addition of quinoline-3-carboxylic acid (0.1 g, 1.1 mmol). The reaction mixture was stirred overnight and allowed to slowly warm to ambient temperature. The solvents were evaporated in vacuo and the residue taken up in ethylacetate and washed successively with water, saturated $NaHCO_3$, a saturated solution of citric acid, water and brine. The organic solution was dried over $MgSO_4$ and then filtered. Solvents were evaporated in vacuo and the crude product subjected to flash chromatography using ethylacetate and hexane as the elutant mixture. The product was isolated as an oil, 0.46 g (74%). MS(CI) m/e 609(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.8-0.96(m,6H) 1.16-1.42(m,12H), 1.45-1.6(m,2H), 1.8-2.0(m,2H), 2.7(m,2H), 3.07-3.45(m,4H), 3.5-3.65(m,2H), 5.15(m,3H), 6.85(d,J=12Hz,1H), 7.2(d,J=9Hz,2H), 7.4(d,J=9Hz,2H), 7.6(m,2H), 7.8(t,J=7Hz,1H), 7.9(t,J=7Hz,1H), 8.15(d,J=9Hz,1H), 8.6(s,1H), 9.35(d,J=3Hz,1H). C,H,N analysis calculated for $C_{34}H_{45}ClN_4O_4$, 0.6 H_2O: C 65.86, H 7.41, N 9.04; found: C 65.63, H 7.29, N 9.42.

Example 63

N-(3'-Quinolylcarbonyl)-3-(2'-Naphthyl)-R-Alanine-di-n-dipentylamide

The reaction was performed in a similar manner to that in example 3 utilizing 75 mg of hydrochloride salt of example 49, quinoline-3-carboxylic acid (34 mg), EDCI (40 mg), HOBt (50 mg), and NMM (22 µL). The oily product was isolated in 31% yield, (32 mg). MS(CI) m/e 510(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.06-1.35(m,12H), 2.85(m,1H), 3.0(m,2H), 3.35(m,2H), 3.55(m,1H), 5.45(apparent q,J=7Hz,1H), 7.32-7.5(m,4H), 7.62(t,J=6Hz,1H), 7.68-7.82(m,5H), 7.88(d,J=7Hz,1H), 8.15(d,J=7z,1H), 8.52(d,J=2Hz,1H).

Example 64

R-(4'-Hydroxyphenyl)-glycine-di-n-pentylamide hydrochloride

The compound was prepared in similar manner to example 2 via deprotection of the product of example 55, using 4 N HCl in dioxane. The oily product was isolated in 90% yield. $[\alpha]_D = -87.0^o$ (c=0.2, MeOH). MS(CI) m/e 307(m+H)$^+$. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.82(m,6H), 1.02-1.2(m,8H), 1.3-1.5(m,4H), 3.05-3.3(m,2H), 3.32-3.4(m,2H), 5.22(bs,1H), 6.83(d,J=9Hz,2H), 7.25(d,J=9Hz,2H), 8.4(bs,3H).

Example 65

N-(3'-Quinolylcarbonyl)-R-(4'-hydroxyphenyl)glycine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 3 utilizing (300 mg, 2.6 mmol) of hydrochloride salt of example 64, quinoline-3-carboxylic acid (450 mg), EDCI (550 mg), HOBt (380 mg), and NMM (0.62 mL). Product was isolated in 53% yield (0.78 g). mp= 79-80^{o}C. $[\alpha]_D$= -99.6^{o} (c=1.0, MeOH). MS(CI) m/e 462(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(t,J=7Hz,6H), 1.1-1.3(m,10H), 1.4-1.5(m,2H), 3.1-3.2(m,2H), 3.25-3.5(m,2H), 5.9(d,J=9Hz,1H), 6.6(d,J=9Hz,2H), 7.25(d,J=9Hz,2H), 7.7(t,J=7Hz,1H), 7.85(t,J=7Hz,1H), 8.08(d,J=9Hz,2H), 8.9(d,J=3Hz,1H), 9.1(d,J=6Hz,1H), 9.25(d,J=3Hz,1H), 9.53(s,1H). C,H,N analysis calculated for $C_{28}H_{35}N_3O_3$: C 72.85, H 7.64, N 9.10; found: C 72.65, H 7.65, N 9.08.

Example 66

N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-(acetyl)-R-Lysine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 33 utilizing 60 mg of the product of example 54 and pyridine with acetic anhydride. The oily product was purified by standard chromatography and isolated in 33% yield (22 mg). $[\alpha]_D$= -1.3^{o} (c=0.5, MeOH). MS(CI) m/e 483(m+H)$^+$. ^{1}H NMR ($CDCl_3$,300MHz) δ 0.92(m,6H), 1.23-1.4(m,8H), 1.45-1.7(m,8H), 1.8(m,2H), 1.98(s,3H), 3.1(m,1H), 3.25(m,2H), 3.32(m,1H), 3.6(m,2H), 5.15(m,1H), 5.85(bs,1H), 7.5(d,J=8Hz,1H), 7.65(t,J=6Hz,1H),

7.82(t,J=6Hz,1H), 7.94(d,J=8Hz,1H), 8.18(d,J=8Hz,1H), 8.62(d,J=2Hz,1H), 9.36(d,2Hz,1H).

Example 67

N-(5'-Hydroxyindolyl-2'-carbonyl)-R-Valine-di-n-pentylamide

The 5-hydroxyindole-2-carboxylic acid (95 mg), hydrochloride of example 2 (150 mg), NMM (0.12 mL), HOBt (70 mg), and EDCI (105 mg) reacted under similar conditions to those described in example 3. The product was isolated in 74% yield. MS(CI) m/e 416(m+H)$^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.9(m,6H), 1.0(apparent q,J=7Hz,6H), 1.32(m,8H), 1.62(m,4H), 2.11(m,1H), 3.15(m,1H), 3.2(m,1H), 3.43(m,1H), 3.62(m,1H), 4.95(m,1H), 5.6(s,1H), 6.78(m,1H), 6.88(dd,J=2,9Hz,1H), 6.98(d,J=9Hz,1H), 7.02(d,J=2Hz,1H), 7.25(d,J=9Hz,1H), 9.3(s,1H).

Example 68

N-(4'-Chlorobenzenesulfonyl)-R-Valine-di-n-pentylamide

The hydrochloride of example 2 (60 mg, 0.22 mmol), NMM (25 μL), was dissolved in 10 mL of CH_2Cl_2 and 4-chlorophenylsulfonyl chloride (46 mg) was added to this reaction mixture and stirred overnight (warming to ambient temperature). The solvent was evaporated in vacuo and ethylacetate and water both in large excess were added to the residue. The organic extracts were successively washed with saturated aqueous $NaHCO_3$, 0.1 HCl solution and brine. The combined extracts were dried over $MgSO_4$,

filtered and concentrated. The product was purified by chromatography using ethylacetate and hexane as elutants. The pure product was isolated in 75% yield (59 mg). mp= 89-90°C. $[\alpha]_D = -61.8°$ (c=0.5, MeOH). MS(CI) m/e 431(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz): δ 0.9(m,12H), 1.15(m,8H), 1.3(m,4H), 1.85(m,1H), 2.9(m,2H), 3.02(m,1H), 3.22(m,1H), 3.8(m,1H), 5.75(d,J=9Hz,1H), 7.43(m,2H), 7.75(m,2H). C,H,N analysis calculated for $C_{21}H_{35}ClN_2O_3S$: C 58.52, H 8.18, N 6.50; found: C 58.56, H 8.22, N 6.48.

Example 69

4-Chlorocinnamic acid N-hydroxysuccinimide ester

To a solution of 4-chlorocinnamic acid (0.8g, 4.38 mmol) in CH_2Cl_2 was added N-hydroxysuccinimide (0.55 g, 4.8 mmol) and EDCI and the reaction mixture was stirred at ambient temperature overnight. The solvents were removed in vacuo and the residue dissolved in ethylacetate and water. Combined EtOAc extracts were dried over $MgSO_4$ and the solution concentrated in vacuo. The residue was crystallized from a mixture of ethylacetate and hexane. The product was isolated in 72% yield (0.88g). mp= 192-193°C. MS(CI) m/e 297(m+NH_4^+). ^{1}H NMR($DMSO_{d6}$,300MHz) δ 2.87(s,4H), 7.05(d,J=17Hz,1H), 7.56(d,J=9Hz,2H), 7.92(d,J=9Hz,2H), 7.99(d,J=17Hz,1H).

Example 70

N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-[E-3'-(4''-chlorophenyl)prop-2'-enoyl]-R-Lysine-di-n-pentylamide

To a solution of example 54 (60 mg, 0.14 mmol) in dimethylformamide (8 mL) cooled to 0°C were added NMM (35 μL) and the active ester of example 69 (40 mg, 0.14 mmol). The mixture was stirred overnight with warming to ambient temperature. The DMF was removed in vacuo and the residue was chromatographed on silica using ethylacetate-hexane as the elutant mixture. The oily product was isolated in 40% yield (35 mg). MS(CI) m/e 605$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.92(m,6H), 1.3(m,8H), 1.62(m,8H), 1.83(m,2H), 3.14(m,1H), 3.35(m,4H), 3.58(m,1H), 5.15(m,1H), 6.18(m,1H), 6.35(d,J=17Hz,1H), 7.25(m,6H), 7.48(d,J=17Hz,1H), 7.62(t,J=8Hz,1H), 7.83(t,J=8Hz,1H), 8.15(d,J=9Hz,1H), 8.62(d,J=2Hz,1H), 9.37(d,J=2Hz,1H).

Example 71

N-(t-Butyloxycarbonyl)-R-Tyrosine-di-n-pentylamide

N-t-Butyloxycarbonyl-R-Tyrosine (4.5 g, 15.4 mmol) was stirred with BOPCl (3.92 g, 15.4 mmol) and dipentylamine (7.9 mL, 39 mmol) in 100 mL of tetrahydrofuran (THF) at 4°C and allowed to warm to room temperature overnight. After one day, additional BOPCl (800 mg) was added and, after two days, the volatiles were evaporated. The residue, dissolved in EtOAc, was extracted with 0.1 M citric acid solution, 0.1 M sodium carbonate (Na_2CO_3) solution, and water; then dried over magnesium sulfate ($MgSO_4$), filtered and concentrated in

vacuo to yield an oil, 5.67 g, 13.4 mmol (87.4%). R_f= 0.45 (2:1 hexanes-EtOAc). $[\alpha]_D = +2.8^o$ (c=0.76, MeOH). MS(CI) m/e 421(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.88(apparent q,J=7Hz,6H), 1.15-1.32(m,10H), 1.36-1.47(m,11H), 2.80-3.07(m,5H), 3.38-3.48(m,1H), 4.72(apparent q,J=6Hz,1H), 5.41(d,J=8Hz,1H), 6.70(d,J=8Hz,2H), 7.02(d,J=8Hz,2H).

Example 72

R-Tyrosine-di-n-pentylamide hydrochloride

The product of example 71 (2.0 g, 4.75 mmol) was dissolved in 4 N HCl in dioxane (20 mL, 80 mmol) that was precooled to 4^{o}C. After 3 hours, the excess reagent was evaporated and the oily residue was placed under high vacuum overnight to yield a glass, 1.5 g, 4.2 mmol (87%). $[\alpha]_D = -42.8^o$ (c=1.2, MeOH). MS(CI) m/e 321(m+H)$^+$. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.82-0.89(m,6H), 1.1-1.4(m,12H), 2.70-3.04(m,5H), 3.37-3.50(m,1H), 4.22(dd,J=5,7Hz,1H), 6.70(d,J=8Hz,2H), 6.99(d,J=8Hz,2H), 8.37(bs,3H), 9.48(s,1H).

Example 73

N,O-Di-(3'-Quinolylcarbonyl)-R-Tyrosine-di-n-pentylamide

The product of example 72 (357 mg, 1 mmol), quinoline-3-carboxylic acid (173 mg, 1 mmol), HOBt (13 mg, 0.1 mmol), and TEA (279 µL, 2 mmol) were dissolved in 10 mL methylene chloride and EDCI (191 mg, 1 mmol) was then added in one portion. After 3 days, the volatiles were evaporated and the residue, in EtOAc, was extracted as in example 71. The residue was then purified by

chromatography on silica gel eluted with 1% ethanol in chloroform to provide first the mono-acylated material (19 mg, see example 80) followed by an oily product, (108 mg, 0.17 mmol, 17% yield). R_f= 0.36 (18:1 chloroform-ethanol). $[\alpha]_D$ = +5.8° (c=0.5, $CHCl_3$). $[\alpha]_D$ = +53.2° (c=0.73, MeOH). MS(CI) m/e 631(m+H)$^+$, 518, 458, 446, 368. ^{1}H NMR($CDCl_3$,300MHz) δ 0.88-0.94(m,6H), 1.22-1.41(m,10H), 1.50-1.59(m,2H), 2.96-3.30(m,5H), 3.52-3.62(m,1H), 5.33-5.42(m,1H), 7.22(d,J=8Hz,1H), 7.30(d,J=8Hz,1H), 7.37(d,J=8Hz,2H), 7.63(dt,J=1,7Hz,1H), 7.68(dt,J=1,7Hz,1H), 7.79-7.93(m,3H), 8.0(dd,J=1,8Hz,1H), 8.16(d,J=8Hz,1H), 8.22(d,J=8Hz,1H), 8.56(d,J=2Hz,1H), 9.02(d,J=2Hz,1H), 9.32(d,J=2Hz,1H), 9.54(d,J=2Hz,1H). C,H,N analysis calculated for $C_{39}H_{42}N_4O_4$, H_2O: C 72.20, H 6.84, N 8.64; found: C 72.38, H 6.62, N 8.50.

Example 74

N-(2'-Indolylcarbonyl)-R-Tyrosine-di-n-pentylamide

The product of example 72 (200 mg, 0.56 mmol), indole-2-carboxylic acid (97 mg, 0.6 mmol) and TEA (84 µL, 0.6 mmol) were dissolved in 5 mL methylene chloride and treated with EDCI (115 mg, 0.6 mmol) at room temperature. After 3 days, the solvent was evaporated and the residue was extracted as in example 71. Column chromatography on silica gel eluted with 1% ethanol in methylene chloride provided product. R_f= 0.38 (18:1 methylene chloride-ethanol). mp= 124-7°C. $[\alpha]_D$ = +21.4° (c=1.17, MeOH). MS(CI) m/e 464(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.88(apparent q,J=8Hz,6H), 1.15-1.56(m,12H), 2.46-3.22(m,5H), 3.48-3.54(m,1H), 5.23-5.32(m,1H), 6.12(s,1H),

6.70(d,J=8Hz,2H), 6.95(d,J=1Hz,1H), 7.05(d,J=8Hz,2H), 7.13(dt,J=1,7Hz,1H), 7.18(d,J=8Hz,1H), 7.27(dt,J=1,7Hz,1H), 7.40(d,J=8Hz,1H), 7.64(d,J=8Hz,1H), 9.22(s,1H). C,H,N analysis calculated for $C_{28}H_{37}N_3O_3$: C 72.54, H 8.05, N 9.06; found: C 72.37, H 8.10, N 8.80.

Example 75

N-(3',4'-Dichlorobenzoyl)-R-Tyrosine-di-n-pentylamide

The product of example 72 (103 mg, 0.29 mmol) was dissolved in 5 mL methylene chloride and treated with 3,4-dichlorobenzoylchloride (126 mg, 0.6 mmol) and TEA (84 µL, 0.6 mmol) at room temperature. After 2 hours, additional acid chloride (13 mg) and TEA (8 µL) were added and the reaction was stirred overnight. The volatiles were evaporated and the residue, in EtOAc, was extracted with 0.1% citric acid, H_2O; then dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting diacylated product residue was dissolved in 10 mL of 1:1 THF-methanol and treated with 1 N NaOH (290 mL, 0.29 mmol). After 1 hour, tlc revealed complete reaction and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc and acidified with 0.1 M citric acid. The EtOAc layer was then washed until neutral, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was warmed with 80% aqueous ethanol and cooled overnight to provide a solid, 64 mg, 0.13 mmol (45% yield). mp= 148-52°C. $[\alpha]_D$ = +15.6° (c=1.0, MeOH). MS(CI) m/e 493$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.88-0.92(m,6H), 1.2-1.6(m,12H), 2.93-3.22(m,5H), 3.50-3.60(m,1H), 5.21-5.28(m,1H), 6.29(s,1H), 6.68(d,J=8Hz,2H), 7.02(d,J=8Hz,2H), 7.15(d,J=8Hz,1H),

7.47(d,J=8Hz,1H), 7.59(dd,J=2,8Hz,1H), 7.91(d,J=2Hz,1H). C,H,N analysis calculated for $C_{26}H_{34}Cl_2N_2O_3$: C 63.28, H 6.94, N 5.68; found: C 63.39, H 7.00, N 5.54.

Example 76

N-(2'-Naphthoyl)-R-Tyrosine-di-n-pentylamide

The product of example 72 (100 mg, 0.28 mmol) was acylated with 2-naphthoic acid (52 mg, 0.30 mmol) in the presence of TEA (39 µL, 0.28 mmol) and EDCI (57 mg, 0.30 mmol) in 5 mL methylene chloride. The reaction and extractive workup were performed as in example 71 to yield 120 mg, 0.25 mmol (89%). mp= 128-133°C. $[\alpha]_D = +11.8^{\circ}$ (c=0.68, MeOH). MS(CI) m/e 475(m+H)$^+$, 303, 290. ^1H NMR(CD_3OD,300MHz) δ 0.88-0.93(m,6H), 1.19-1.38(m,9H), 1.44-1.62(m,3H), 2.99(dd,J=7,13Hz,1H), 3.08-3.29(m,4H), 3.37-3.47(m,1H), 5.22(dd,J=7,9Hz,1H), 6.72(d,J=8Hz,2H), 7.13(d,J=8Hz,2H), 7.53-7.62(m,2H), 7.84(dd,J=2,9Hz,1H), 7.90-7.99(m,3H), 8.37(s,1H). C,H,N analysis calculated for $C_{30}H_{38}N_2O_3$: C 75.91, H 8.07, N 5.90; found: C 75.57, H 7.97, N 5.83.

Example 77

N-t-Butyloxycarbonyl-(O-benzyl)-R-Tyrosine-di-n-pentylamide

N-t-Butyloxycarbonyl-(O-benzyl)-R-Tyrosine (3.71 g, 10 mmol) was stirred with di-n-pentylamine (5.1 mL, 25 mmol), HOBt (1.4 g, 10 mmol) and TEA (1.4 mL, 10 mmol) in 150 mL methylene chloride at 4°C and then BOPCl (2.6 g, 10 mmol) was added. The reaction was allowed to reach room temperature overnight. After one day, additional BOPCl

(260 mg) and TEA (140 µL) were added. After 2 days, the volatiles were evaporated and the residue (in EtOAc) was extracted with 0.1 M H_3PO_4, 0.1 M Na_2CO_3, H_2O; then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluted with 2:1 hexanes-EtOAc to yield an oil, 1.3 g, 2.55 mmol (25%). $[\alpha]_D$ = +5.8^o (c=1.5, MeOH). MS(CI) m/e 511(m+H)$^+$, 456, 393. ^{1}H NMR($CDCl_3$,300MHz) δ 0.84-0.93(m,6H), 1.1-1.35(m,12H), 1.41(s,9H), 2.81-3.04(m,5H), 3.36-3.46(m,1H), 4.15-4.23(m,1H), 5.03(s,2H), 5.32(d,J=8Hz,1H), 6.87(d,J=8Hz,2H), 7.11(d,J=8Hz,2H), 7.32-7.43(m,5H).

Example 78

(O-Benzyl)-R-Tyrosine-di-n-pentylamide hydrochloride

The product of example 77 (1.3 g, 2.55 mmol) was treated with 5 mL of 4 N HCl in dioxane, precooled to 4^{o}C. The reaction mixture was then allowed to reach room temperature. After 1 hour tlc revealed complete reaction and the excess reagent was evaporate. The residue was placed under high vacuum overnight to yield an oil, 1.2 g. R_f= 0.59 (80:20:1 chloroform-methanol-ammonium hydroxide). $[\alpha]_D$ = -32.5^o (c=2.2, MeOH). MS(CI) m/e 411(m+H)$^+$. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.85(apparent q,J=7Hz,6H), 1.07-1.38(m,12H), 2.68-2.97(m,4H), 3.05(dd,J=5,13Hz,1H), 3.32-3.42(m,2H), 4.27(dd,J=5,8Hz,1H), 5.09(s,2H), 6.93(d,J=8Hz,2H), 7.12(d,J=8Hz,2H), 7.32-7.43(m,5H), 8.37(s,3H).

Example 79

N-(3'-Quinolylcarbonyl)-(O-benzyl)-R-Tyrosine-di-n-pentylamide

EDCI (290 mg, 1.5 mmol) was added to a cooled (4°C) solution of quinoline-3-carboxylic acid (260 mg, 1.5 mmol), the product of example 78 (650 mg, 1.35 mmol), and TEA (418 µL, 3.0 mmol) in 5 mL methylene chloride. The stirred reaction mixture was allowed to warm to room temperature overnight. After evaporation of the volatiles, the residue was dissolved in EtOAc and extracted with 0.1 M H_3PO_4 (3x), 0.1 M Na_2CO_3 (3x), brine (3x); then dried over $MgSO_4$, filtered and concentrated in vacuo to yield an oil, 650 mg, 1.15 mmol (85%). R_f= 0.77 (18:1 chloroform-ethanol), 0.40 (1:1 hexanes-EtOAc). $[\alpha]_D$ = +0.21° (c=0.47, $CHCl_3$). MS(FAB) m/e 566(m+H)$^+$, 393, 381. ^{1}H NMR($CDCl_3$,300MHz) δ 0.91(apparent q,J=7Hz,6H), 1.17-1.38(m,10H), 1.43-1.6(m,2H), 2.86-3.17(m,5H), 3.49-3.59(m,1H), 5.03(s,2H), 5.26-5.33(m,1H), 6.90(d,J=8Hz,2H), 7.16(d,J=8Hz,2H), 7.28-7.43(m,6H), 7.62(dt,J=1,7Hz,1H), 7.82(dt,J=1,8Hz,1H), 7.90(d,J=8Hz,1H), 8.18(d,J=8Hz,1H), 8.54(d,J=2Hz,1H), 9.32(d,J=2Hz,1H). C,H,N analysis calculated for $C_{36}H_{43}N_3O_3$: C 76.55, H 7.88, N 7.29; found: C 76.43, H 7.66, N 7.43.

Example 80

N-(3'-Quinolylcarbonyl)-R-Tyrosine-di-n-pentylamide

The product of example 79 (614 mg, 1.09 mmol) was dissolved in 30 mL methanol and treated with 10% Pd/C (200 mg, pre-wetted with solvent under nitrogen) under 1

atmosphere hydrogen gas. Another 200 mg of catalyst was added after 4 hours and the reaction mixture was stirred overnight. The mixture was then filtered and the filtrate concentrated in vacuo. Silica gel column chromatography of the residue (eluted with a 2:1 to 1:1 hexane-EtOAc step gradient) provided 270 mg, 0.57 mmol (52% yield). mp= 135-37^{o}C. $[\alpha]_D = +12.6^{o}$ (c=0.5, MeOH). MS(CI) m/e 476$(m+H)^+$, 347, 321, 291. ^{1}H NMR($CDCl_3$,300MHz) δ 0.91(t,J=7Hz,6H), 1.24-1.38(m,8H), 1.48-1.62(m,4H), 3.0-3.28(m,5H), 3.51-3.61(m,1H), 5.30-5.38(m,1H), 6.72(d,J=8Hz,2H), 6.78(s,1H), 7.06(d,J=8Hz,2H), 7.38(d,J=8Hz,1H), 7.60(t,J=7Hz,1H), 7.80(dt,J=1,7Hz,1H), 7.88(d,J=8Hz,1H), 8.15(d,J=9Hz,1H), 8.58(d,J=2Hz,1H), 9.27(d,J=2Hz,1H). C,H,N analysis calculated for $C_{29}H_{37}N_3O_3$: C 73.23, H 7.84, N 8.83; found: C 73.23, H 7.89, N 8.76.

Example 81

N-(3'-Quinolylcarbonyl)-(O-bisulfatyl)-R-Tyrosine di-n-pentylamide ammonium salt

The product of example 80 (59 mg, 0.12 mmol) was dissolved in 2 mL DMF and treated with freshly prepared pyridine-sulfur trioxide complex (H.C.Reitz et al *J. Amer. Chem. Soc.* *68*, 1031-5, **1946**) overnight at room temperature. The pyridine was evaporated in vacuo and the DMF solution was poured into water and the pH adjusted to 7 with 1 N NaOH. The homogeneous solution was then frozen and lyophilized. Preparative C-18 chromatography of the residue eluted with a gradient from 100% aqueous buffer (0.05 M ammonium acetate, pH 6.2) to 50%

acetonitrile/aqueous buffer over 10 minutes provided product fractions which were pooled, frozen and lyophilized to yield 48 mg, 0.08 mmol (67%). mp= 113-6°C. $[\alpha]_D$ = +12.2° (c=0.88, MeOH). MS(FAB) m/e 554(m-H)$^+$, 368, 302, 298. ^1H NMR(D_2O,300MHz) δ 0.68-0.75(m,6H), 0.98-1.43(m,12H), 2.98-3.28(m,6H), 5.22(t,J=7Hz,1H), 7.24(d,J=8Hz,2H), 7.30(d,J=8Hz,2H), 7.44(t,J=8Hz,1H), 7.62(d,J=8Hz,1H), 7.69(t,J=8Hz,1H), 7.82(d,J=8Hz,1H), 8.36(s,1H), 8.78(s,1H). C,H,N analysis calculated for $C_{29}H_{40}N_4O_6S$, 0.50 H_2O: C 59.88, H 7.10, N 9.63; found: C 59.77, H 6.82, N 9.11.

Example 82

(a)

3,5-Di-iodo-N-(3'-quinolylcarbonyl)-R-Tyr-di-n-pentylamide

(b)

3-Iodo-N-(3'-quinolylcarbonyl)-R-Tyr-di-n-pentylamide

Iodine (27 mg, 0.11 mmol) was mixed with morpholine (40 µL, 0.46 mmol) in 5 mL methanol and added to the product of example 80 (50 mg, 0.11 mmol) in 15 mL methanol at room temperature. The reaction was stirred until tlc indicated complete reaction. After evaporation of the solvent, chromatography of the residue on silica gel eluted with a step gradient of chloroform to 1% ethanol in chloroform provided first the diiodo product followed by the monoiodo compound. Diiodo product (a): $[\alpha]_D$ = +18° (c=0.11, MeOH). MS(CI) m/e 728(m+H)$^+$, 602. ^1H NMR($CDCl_3$,300MHz) δ 0.92(apparent q,J=7Hz,6H), 1.2-1.45(m,12H), 2.92-3.13(m,5H), 3.53-3.67(m,1H), 5.22-

5.28(m,1H), 5.72(s,1H), 7.27(d,J=7Hz,1H), 7.56(s,2H), 7.63(dt,J=1,8Hz,1H), 7.83(dt,J=1,8Hz,1H), 7.93(d,J=8Hz,1H), 8.18(d,J=8Hz,1H), 8.55(d,J=2Hz,1H), 9.33(d,J=2Hz,1H). C,H,N analysis calculated for $C_{29}H_{35}I_2N_3O_3$, 0.4 EtOAc: C 48.19, H 5.05, N 5.51; found: C 48.43, H 5.03, N 5.79. Monoiodo product (b): mp= 75-85°C. MS(CI) m/e 602(m+H)$^+$. ^{1}H NMR($CDCl_3$,500MHz) δ 0.84(apparent q,J=7Hz,6H), 1.13-1.35(m,9H), 1.37-1.53(m,3H), 2.90-2.98(m,3H), 3.02-3.08(m,2H), 3.48-3.55(m,1H), 5.18-5.23(m,1H), 6.83(d,J=8Hz,1H), 7.05(dd,J=1,3Hz,1H), 7.22(d,J=8Hz,1H), 7.46(d,J=2Hz,1H), 7.57(dt,J=1,8Hz,1H), 7.76(dt,J=1,8Hz,1H), 7.84(d,J=8Hz,1H), 8.10(d,J=8Hz,1H), 8.48(d,J=2Hz,1H), 9.24(d,J=2Hz,1H). C,H,N analysis calculated for $C_{29}H_{36}IN_3O_3$, 1.5 H_2O: C 55.42, H 6.25, N 6.69; found: C 55.19, H 5.95, N 6.17.

Example 83

N-(3'-Quinolylcarbonyl)-(O-methyl)-R-Tyrosine-di-n-pentylamide

The product of example 80 (25 mg, 0.053 mmol) was dissolved in 1 mL acetone and K_2CO_3 (8 mg, 0.058 mmol) and methyl iodide (5 μL, 0.08 mmol) were added. After 3 hours at reflux, additional methyl iodide (5 mL) and acetone (2 mL) were added. After 2 days, the volatiles were evaporated and the residue, in EtOAc, was extracted with 0.1% aqueous citric acid, water; then dried over $MgSO_4$, filtered and concentrated in vacuo. MS(CI) m/e 490(m+H)$^+$, 476, 361, 347, 317. ^{1}H NMR($CDCl_3$,300MHz) δ 0.86-0.93(m,6H), 1.2-1.56(m,12H), 2.42-3.15(m,5H), 3.49-

3.59(m,1H), 3.78(s,3H), 5.27-5.34(m,1H), 6.77(d,J=8Hz,1H), 6.82(d,J=8Hz,1H), 7.08(d,J=8Hz,1H), 7.16(d,J=8Hz,1H), 7.41-7.46(m,1H), 7.56-7.63(m,1H), 7.76-7.82(m,1H), 7.83-7.88(m,1H), 8.14(d,J=8Hz,1H), 8.53(d,J=2Hz,1H), 9.29(t,J=2Hz,1H).

Example 84

Methyl N-t-Butyloxycarbonyl-(O-benzyl)-R-Tyrosyl-S-phenylglycinate

N-t-Butyloxycarbonyl-(O-benzyl)-R-Tyrosine (1.0 g, 2.7 mmol), methyl S-phenylglycinate hydrochloride (540 mg, 2.7 mmol), HOBt (362 mg, 2.7 mmol) and TEA (374 µL, 2.7 mmol) were dissolved in 20 mL THF and treated with BOPCl (682 mg, 2.7 mmol). The reaction was followed by tlc (18:1 chloroform-ethanol) and additional BOPCl (200 mg) and TEA (374 µL) were added after 1,2 and 4 days. Methylene chloride (20 mL) also was added after 2 days. After 1 week, the volatiles were evaporated in vacuo and the residue, in EtOAc, was extracted as in example 71. Chromatography of the residue on silica gel eluted with a step gradient from 9:1 to 2:1 hexanes-EtOAc yielded 485 mg, 1.13 mmol (42%). mp= 138-39°C. $[\alpha]_D$ = +48.7° (c=1.0, MeOH). MS(CI) m/e 519$(m+H)^+$, 463, 419. ^1H NMR($CDCl_3$,300MHz) δ 1.41(s,9H), 2.92-3.04(m,2H), 3.71(s,3H), 4.35(bs,1H), 5.01(s,3H), 5.43-5.46(m,1H), 6.78(d,J=7Hz,1H), 6.82(d,J=8Hz,2H), 7.02(d,J=8Hz,2H), 7.19-7.23(m,1H), 7.30-7.45(m,10H).

Example 85

Methyl (O-Benzyl)-R-Tyrosyl-S-phenylglycinate hydrochloride

The product of example 84 (450 mg, 1.05 mmol) was dissolved in 4 N HCl in dioxane (5 mL, 20 mmol) precooled to 4^{o}C. After 1 hour, the excess reagent was evaporated in vacuo and the product used directly in the next step. mp= 163-6^{o}C. $[\alpha]_D$ = +43.7^{o} (c=0.76, MeOH). MS(FAB) m/e 419(m+H)$^+$, 403, 226. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 2.86-3.00(m,2H), 3.67(s,3H), 4.13(bt,J=5Hz,1H), 5.03(s,2H), 5.45(d,J=7Hz,1H), 6.88(d,J=8Hz,2H), 7.05(d,J=8Hz,2H), 7.22-7.25(m,2H), 7.33-7.46(m,8H), 8.28(s,3H), 9.35(d,J=7Hz,1H).

Example 86

Methyl N-(3'-Quinolylcarbonyl)-(O-benzyl)R-Tyrosyl-S-phenylglycinate

Quinoline-3-carboxylic acid (182 mg, 1.05 mmol), TEA (146 µL, 1.05 mmol) and the product of example 85 (1.05 mmol) were dissolved in 20 mL methylene chloride and EDCI (201 mg, 1.05 mmol) was added at ambient temperature. After 4 days, the volatiles were evaporated and the residue was extracted as in example 71. The solvents were evaporated in vacuo to provide 407 mg, 0.71 mmol (68% yield). mp= 153-8^{o}C. $[\alpha]_D$ = +73.0^{o} (c=1.2, $CHCl_3$-MeOH/1:1). MS(FAB) m/e 574(m+H)$^+$, 419, 381. ^{1}H NMR($CDCl_3$,300MHz) δ 3.06(dd,J=8,14Hz,1H), 3.20(dd,J=5,14Hz,1H), 3.70(s,3H), 4.94-5.02(m,3H), 5.53(d,J=7Hz,1H), 6.78(d,J=8Hz,2H), 6.83(d,J=7Hz,1H),

7.01(d,J=8Hz,2H), 7.14(d,J=7Hz,1H), 7.20-7.23(m,2H), 7.33-7.36(m,4H), 7.39-7.44(m,4H), 7.62(dt,J=1,7Hz,1H), 7.82(dt,J=1,7Hz,1H), 7.88(d,J=8Hz,1H), 8.15(d,J=8Hz,1H), 8.54(d,J=2Hz,1H), 9.28(d,J=2Hz,1H). C,H,N analysis calculated for $C_{35}H_{31}N_3O_5$, 0.5 H_2O: C 72.15, H 5.54, N 7.21; found: C 72.05, H 5.63, N 6.88.

Example 87

Methyl N-(3'-Quinolylcarbonyl)-R-Tyrosyl-S-phenylglycinate

The product of example 86 (200 mg, 0.35 mmol) was dissolved in 10 mL methylene chloride and treated with trimethylsilyliodide (TMSI, 198 µL, 1.39 mmol) at room temperature. Additional TMSI (198 µL) was added after 1 day. After 3 days, the reaction was quenched with methanol for 5 minutes and then poured into 0.1 M citric acid and extracted with ethylacetate (3x). The combined ethylacetate solution was washed with water; then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude solid was purified by chromatography on silica gel eluted with a step gradient of 1 to 5% ethanol in methylene chloride and then crystallized from EtOAc and hexane to yield 51 mg (30%). mp= 238-40°C. $[\alpha]_D$ = +72.6° (c=0.23, MeOH). MS(CI) m/e 484(m+H)$^+$, 319. ^{1}H NMR($CDCl_3$-CD_3OD,300MHz) δ 3.0-3.16(m,2H), 3.72(s,3H), 4.92-5.01(m,1H), 5.50(d,J=7Hz,1H), 6.67(d,J=8Hz,2H), 6.99(d,J=8Hz,2H), 7.21-7.24(m,2H), 7.35-7.38(m,3H), 7.40(s,1H), 7.68(dt,J=1,7Hz,1H), 7.86(dt,J=1,7Hz,1H), 7.98(d,J=8Hz,1H), 8.12(d,J=8Hz,1H), 8.14(d,J=6Hz,1H), 8.22(d,J=8Hz,1H), 8.68(d,J=2Hz,1H), 9.21(d,J=2Hz,1H).

C,H,N analysis calculated for $C_{28}H_{25}N_3O_5$: C 69.55, H 5.21, N 8.69; found: C 69.20, H 5.29, N 8.60.

Example 88

N'-Benzyloxycarbonyl-(2,R)-aminobutyrolactone

N-Benzyloxycarbonyl-R-methionine (283 mg, 1.0 mmol) and α-iodo acetamide (555 mg, 3.0 mmol) were dissolved in 6 mL of 50% aqueous ethanol and warmed to 4°C for 4 days. Citric acid was added (3 mL of a 0.1 M solution) and the mixture was refluxed for 4 hours. After evaporation of the volatiles, the residue was poured into water and extracted with ethyl acetate (3x). The combined ethylacetate solution was extracted with 0.5 N HCl, water; then dried and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluted with 1:1 hexanes-ethylacetate to yield 106 mg, 0.52 mmol (52%). (cf: Ozinskas, A.J., Rosenthal, G.A., J. Organic Chem. 51, 5047, 1986). mp= 124-5°C. $[\alpha]_D$ = +31.3° (c=1.2, MeOH). ^1H NMR($CDCl_3$,300MHz) δ 2.16-2.28(m,1H), 2.76-2.86(m,1H), 4.2-4.31(m,1H), 4.37-4.50(m,2H), 5.13(s,2H), 5.32(bs,1H), 7.32-7.38(m,5H).

Example 89

N-Benzyloxycarbonyl-Homoserine-di-n-pentylamide

The product of example 88 (620 mg, 2.8 mmol) and dipentylamine (1.4 mL, 7 mmol) were dissolved in 60 mL acetonitrile and then heated to reflux overnight. After evaporation of the volatiles, the residue was chromatographed on silica gel eluted with a step gradient from chloroform to 1% ethanol in chloroform to yield an

oil, 580 mg, 1.6 mmol (56%). $[\alpha]_D$ = +0.31° (c=0.96, MeOH). MS(CI) m/e 393(m+H)$^+$, 253, 236, 192. ^{1}H NMR($CDCl_3$,300MHz) δ 0.87-0.93(m,6H), 1.22-1.38(m,8H), 1.47-1.63(m,4H), 1.86-1.97(m,1H), 3.01-3.20(m,2H), 3.34-3.43(m,2H), 3.52-3.72(m,4H), 4.76(dt,J=3,11Hz,1H), 5.1(d,J=12Hz,1H), 5.13(d,J=12Hz,1H), 5.93(d,J=8Hz,1H), 7.31-7.38(m,5H).

Example 90

N'-(2'-Indolylcarbonyl)-(2,RS)-aminobutyrolactone

EDCI (191 mg, 1.0 mmol) was added to a solution of indole-2-carboxylic acid (161 mg, 1.0 mmol), α-aminobutyrolactone hydrobromide (182 mg, 1.0 mmol), HOBt (135 mg, 1.0 mmol), and TEA (279 µL, 2.0 mmol) in 15 mL methylene chloride at room temperature. Additional EDCI (120 mg) and TEA (56 µL) were added after 1 day. After 5 days, the volatiles were evaporated and the residue, in EtOAc, was extracted with 1 M H_3PO_4, 0.1 M Na_2CO_3, and brine. The solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The product was crystallized from EtOAc to yield 147 mg, 0.6 mmol, 60%. R_f= 0.17 (1:1 hexanes-EtOAc). mp= 235-6°C. MS(CI) m/e 245(m+H)$^+$, 144. ^{1}H NMR($CDCl_3$-CD_3OD,300MHz) δ 1.86-2.51(m,1H), 2.19-2.79(m,1H), 4.32-4.42(m,1H), 4.56(dt,J=2,11Hz,1H), 4.82(dd,J=8,11Hz,1H), 7.1-7.15(m,2H), 7.28(dt,J=1,8Hz,1H), 7.40(s,0.5 H), 7.46(d,J=8Hz,1H), 7.66(d,J=8Hz,1H).

Example 91

N-(2'-Indolylcarbonyl)-R,S-Homoserine-di-n-pentylamide

The product of example 90 (25 mg, 0.1 mmol) and dipentylamine (50 µL, 0.25 mmol) were dissolved in 2 mL THF and warmed to 50°C. Additional dipentylamine (250 µL) was added after several hours. After 4 days, the volatiles were evaporated and the residue was chromatographed on silica eluted with 2:1 hexanes-EtOAc. Yield: 26 mg, 0.06 mmol, 60%. mp= 128-139°C. MS(CI) m/e 402$(m+H)^+$, 158. ^1H NMR($CDCl_3$,300MHz) δ 0.92(t,J=7Hz,6H), 1.26-1.42(m,10H), 1.52-1.72(m,3H), 1.98-2.11(m,1H), 2.69(t,J=8Hz,1H), 3.06-3.26(m,2H), 3.42-3.52(m,1H), 3.60-3.77(m,3H), 5.12-5.20(m,1H), 7.03(d,J=1Hz,1H), 7.16(dt,J=1,8Hz,1H), 7.31(dt,J=1,7Hz,1H), 7.42(dd,J=1,8Hz,1H), 7.48(d,J=8Hz,1H), 7.67(d,J=8Hz,1H), 9.13(s,1H). C,H,N analysis calculated for $C_{23}H_{35}N_3O_3$, 0.5 H_2O: C 67.28, H 8.84, N 10.24; found: C 67.42, H 8.64, N 10.10.

Example 92

N'-(3'-Quinolylcarbonyl)-(2,RS)-aminobutyrolactone

Quinoline-3-carboxylic acid (5.2 g, 30 mmol) was coupled to α-aminobutyrolactone (5.5 g, 30 mmol) in a manner similar to that in example 90 to provide 2.62 g, 10.2 mmol (34% yield). Additional extraction of the aqueous layer with EtOAc yielded another 820 mg, 3.2 mmol (10.7%). R_f= 0.26 (18:1 chloroform-ethanol). mp= 160-63°C. MS(CI) m/e 257$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 2.32-2.46(m,1H), 2.91-3.01(m,1H), 4.35-4.43(m,1H),

4.56(dt,J=2,10Hz,1H), 4.83-4.92(m,1H), 7.36(d,J=6Hz,1H), 7.60(dt,J=1,8Hz,1H), 7.81(dt,J=2,8Hz,1H), 7.86(d,J=8Hz,1H), 8.12(dd,J=1,8Hz,1H), 8.59(dd,J=1,2Hz,1H), 9.28(d,J=2Hz,1H). C,H,N analysis calculated for $C_{14}H_{12}N_2O_3$: C 65.61, H 4.72, N 10.93; found: C 65.42, H 4.82, N 10.82.

Example 93

N-(3'-Quinolylcarbonyl)-R,S-Homoserine-di-n-pentylamide

The product of example 92 (500 mg, 2.0 mmol) was treated with dipentylamine (1.5 mL, 7.4 mmol) in 25 mL of toluene and refluxed. After 2 days, an additional 1 mL of dipentylamine was added and the heating was continued. After 1 week, the volatiles were evaporated in vacuo and the excess amine was removed by Kugelrohr distillation. The residue was then chromatographed on silica gel eluted with a step gradient of chloroform to 4% ethanol in chloroform to yield an oil, 611 mg, 1.48 mmol (74%). MS(CI) m/e 414$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 0.88-0.95(m,6H), 1.25-1.42(m,7H), 1.52-1.75(m,5H), 2.04-2.15(m,1H), 3.06-3.28(m,2H), 3.46-3.57(m,2H), 3.62-3.81(m,3H), 4.01(dd,J=5,9Hz,1H), 5.21-5.28(m,1H), 7.63(dt,J=1,8Hz,1H), 7.72(d,J=7Hz,1H), 7.83(dt,J=1,8Hz,1H), 7.93(dd,J=1,7Hz,1H), 8.18(d,J=8Hz,1H), 8.62(d,J=2Hz,1H), 9.37(d,J=3Hz,1H). C,H,N analysis calculated for $C_{24}H_{35}N_3O_3$, 0.25 H_2O: C 68.95, H 8.56, N 10.05; found: C 69.26, H 8.45, N 10.06.

Example 94

N-(3'-Quinolylcarbonyl)-R,S-Homoserine-n-pentylamide

The product of example 92 (200 mg, 0.8 mmol) and n-pentylamine (232 µL, 2.0 mmol) were dissolved in 20 mL of 1:1 THF-acetonitrile and stirred at room temperature until starting material was consumed (tlc: R_f= 0.15, 18:1 chloroform-ethanol). The volatiles were evaporated in vacuo. The residue was mixed with hexanes and the product filtered away to yield 273 mg, 0.79 mmol (99%). mp= 181-3°C. MS(CI) m/e 344(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.91(t,J=7Hz,3H), 1.30-1.38(m,4H), 1.51-1.58(m,2H), 1.95-2.04(m,1H), 2.12-2.21(m,1H), 3.25-3.36(m,2H), 3.80(bs,2H), 4.26(bs,1H), 4.83-4.90(m,1H), 7.37(bt,J=3Hz,1H), 7.64(dt,J=1,5Hz,1H), 7.83(dt,J=1,6Hz,1H), 7.93(d,J=6Hz,1H), 8.10(d,J=6Hz,1H), 8.15(d,J=7Hz,1H), 8.68(d,J=2Hz,1H), 9.37(d,J=1Hz,1H). C,H,N analysis calculated for $C_{19}H_{25}N_3O_3$, 0.25 $CHCl_3$: C 61.13, H 6.82, N 11.26; found: C 60.82, H 6.88, N 11.16.

Example 95

N-t-Butyloxycarbonyl-R-Methionine-di-n-pentylamide

BOPCl (5.1 g, 20 mmol) was added to a cooled solution (4°C) of N-t-Butyloxycarbonyl-R-Methionine (5.0 g, 20 mmol), dipentylamine (8.0 mL, 40 mmol), in 60 mL of dry THF and the stirred reaction was allowed to attain room temperature overnight. The volatiles were evaporated in vacuo. The residue was dissolved in EtOAc and extracted successively with 1 M H_3PO_4 (3x), 1 M Na_2CO_3 (3x), brine (3x); then dried over $MgSO_4$, filtered and concentrated in

vacuo to yield an oil: 4.6 g, 11.7 mmol (59%). R_f = 0.81 (1:1 hexanes-EtOAc). $[\alpha]_D$ = +27.5^o (c=2.7, MeOH). MS(CI) m/e 389(m+H)$^+$, 333, 311, 258, 219, 202, 158. ^{1}H NMR($CDCl_3$,300MHz) δ 0.86-0.93(m,6H), 1.21-1.37(m,9H), 1.42(s,9H), 1.43-1.66(m,3H), 1.76-1.96(m,2H), 2.11(s,3H), 2.54(t,J=7Hz,2H), 3.06-3.15(m,1H), 3.19-3.29(m,1H), 3.32-3.42(m,1H), 3.46-3.56(m,1H), 4.68-4.75(m,1H), 5.37(d,J=9Hz,1H).

Example 96

N-(3'-Quinolylcarbonyl)-(O-methyl)-R,S-Homoserine-di-n-pentylamide

The product of example 93 was methylated in a similar manner to that in example 34 to provide the title compound after purification by chromatography.

Example 97

N-(3'-Quinolylcarbonyl)-(O-benzyl)-R,S-Homoserine-di-n-pentylamide

The product of example 93 was benzylated in a manner similar to that in example 34 utilizing benzyl bromide as the alkylating agent. The title compound was provided after purification by chromatography.

Example 98

R-Methionine-di-n-pentylamide trifluoroacetate salt

The product of example 95 (4 g, 10.3 mmol) was dissolved in 30 mL trifluoroacetic acid precooled to 4^{o}C. After 2 hours, the excess reagent was evaporated and the residue was placed under high vacuum overnight. $[\alpha]_D$ =

+5.1° (c=1.4, MeOH). MS(CI) m/e 289(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.88(apparent q,J=8Hz,6H), 1.18-1.35(m,8H), 1.42-1.58(m,4H), 1.89-1.96(bm,2H), 2.08(s,3H), 2.43-2.67(m,2H), 3.00-3.09(m,1H), 3.13-3.23(m,1H), 3.28-3.38(m,1H), 3.48-3.57(m,1H), 4.2-4.28(m,1H), 8.17(s,3H).

Example 99

N-(3'-Quinolylcarbonyl)-R-Methionine-di-n-pentylamide

Quinoline-3-carboxylic acid (0.43 g, 2.5 mmol), the product of example 98 (1.0 g, 2.5 mmol), and TEA (697 µL, 5 mmol) were dissolved in 15 mL of methylene chloride cooled to 4°C and EDCI (0.48 mg, 2.5 mmol) was added. The stirred reaction mixture was allowed to attain room temperature overnight. The volatiles were evaporated and the residue in EtOAc was extracted with 0.1 M citric acid, 0.1 M Na_2CO_3, water; then dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography of the residue eluted with a step gradient of chloroform to 0.5% ethanol in chloroform yielded an oil, 572 mg, 1.29 mmol (52%). R_f= 0.19 (1:1 hexanes-ethylacetate). $[\alpha]_D$ = +8.0° (c=0.85, MeOH). MS(CI) m/e 444(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.91(t,J=7Hz,3H), 0.93(t,J=7Hz,3H), 1.23-1.42(m,8H), 1.52-1.62(m,2H), 1.63-1.75(m,2H), 2.02-2.17(m,5H), 2.56-2.72(m,2H), 3.10(t,J=8Hz,0.5H), 3.14(t,J=8Hz,0.5H), 3.25-3.35(m,1H), 3.46-3.55(m,1H), 3.59(t,J=8Hz,0.5H), 3.63(t,J=8Hz,0.5H), 5.28-5.36(m,1H), 7.55(d,J=8Hz,1H), 7.12(dt,J=1,7Hz,1H), 7.81(dt,J=1,8Hz,1H), 7.88(dd,J=1,8Hz,1H), 8.15(d,J=8Hz,1H), 8.54(d,J=2Hz,1H), 9.33(d,J=2Hz,1H).

C,H,N analysis calculated for $C_{25}H_{37}N_3O_2S$, 0.5 H_2O: C 66.33, H 8.46, N 9.28; found: C 66.33, H 8.13, N 9.25.

Example 100

N-(3'-Quinolylcarbonyl)-R-Methioninesulfoxide-di-n-pentylamide

The product of example 99 (100 mg, 0.23 mmol) was dissolved in 5 mL THF and m-chloroperbenzoic acid (47 mg, 0.23 mmol) was added at room temperature. The reaction was stirred overnight. The volatiles were evaporated and the residue, in EtOAc, was extracted with water until the aqueous extract was neutral (pH=7); then the solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel eluted with methylene chloride and ethanol to provide the product as an oil. $[\alpha]_D = 8.8^o$ (c=0.73, MeOH). MS(CI) m/e 460$(m+H)^+$, 396. ^1H NMR($CDCl_3$,300MHz) δ 0.92(apparent q,J=7Hz,6H), 1.26-1.40(m,10H), 1.52-1.73(m,3H), 2.14-2.26(m,1H), 2.39-2.52(m,1H), 2.71-3.02(m,3H), 3.08-3.18(m,1H), 3.23-3.35(m,1H), 3.38-3.52(m,1H), 3.58-3.68(m,1H), 5.20-5.34(m,1H), 7.62(tt,J=1,8Hz,2H), 7.72(d,J=7Hz,1H), 7.83(tt,J=1,8Hz,1H), 7.92(d,J=8Hz,1H), 8.17(d,J=8Hz,1H), 8.62(dd,J=2,5Hz,1H), 9.35(dd,J=2,3Hz,1H). C,H,N analysis calculated for $C_{25}H_{37}N_3O_3S$, 0.1 EtOAc: C 65.13, H 8.13, N 8.97; found: C 65.31, H 8.30, N 8.73.

Example 101

N-t-Butyloxycarbonyl-R-Proline-di-n-pentylamide

BOPCl (1.18 g, 4.64 mmol) was added to a cooled solution (4°C) of N-t-Butyloxycarbonyl-R-Proline (1.0 g, 4.64 mmol), dipentylamine (2.5 mL, 12.5 mmol), in 50 mL of dry THF. The cooling bath was removed and the stirred reaction mixture was allowed to warm to ambient temperature gradually. After 5 hours, the volatiles were evaporated in vacuo. The residue was dissolved in EtOAc and extracted successively with 1 M H_3PO_4 (3x), 1 M Na_2CO_3 (3x), brine (3x); then dried over $MgSO_4$, filtered and concentrated in vacuo to yield an oil, 880 mg, 2.48 mmol (54%). R_f= 0.28 (2:1 hexanes-EtOAc). $[\alpha]_D$ = +28.7° (c=1.0, MeOH). MS(CI) m/e 355(m+H)$^+$, 299, 255. ^{1}H NMR($CDCl_3$,300MHz) δ 0.84-0.94(m,6H), 1.23-1.38(m,8H), 1.41(s,6H), 1.45(s,3H), 1.49-1.58(m,6H), 1.80-1.90(m,1H), 2.0-2.23(m,1H), 3.12-3.33(m,4H), 3.4-3.52(m,1H), 3.56-3.67(m,1H), 4.44(dd,J=4,8Hz,0.6H), 4.58(dd,J=2,8Hz,0.4H).

Example 102

R-Proline-di-n-pentylamide hydrochloride

The product of example 101 (800 mg, 2.3 mmol) was mixed with HCl-Dioxane (12.5 mL, 50 mmol, pre-cooled to 4°C) under an N_2 atmosphere at ambient temperature. After 1 hour, the volatiles were evaporated in vacuo and the residue was mixed with toluene and concentrated (twice) then placed under high vacuum overnight. The residue was utilized directly.

Example 103

N-(2'-Indolylcarbonyl)-R-Proline-di-n-pentylamide

EDCI (440 mg, 2.3 mmol) was added to a cooled (4°C) solution of indole-2-carboxylic acid (371 mg, 2.3 mmol), the product of example 102 (2.3 mmol assumed), HOBt (311 mg, 2.3 mmol), and TEA (321 μL, 2.3 mmol) in 10 mL methylene chloride. The stirred reaction was allowed to attain ambient temperature overnight. The volatiles were evaporated and the residue was dissolved in EtOAc and extracted with 1 M H_3PO_4 (3x), 1 M Na_2CO_3 (3x), brine (3x); then dried over $MgSO_4$, filtered and concentrated to an orange oil. The crude product was purified by chromatography on silica eluted with 2:1 hexanes-EtOAc to yield 0.92 g, 2.4 mmol (92%) as a slightly yellow glass. R_f= 0.22 (2:1 hexanes-EtOAc). The glass was dissolved in hot hexanes-EtOAc, then cooled slowly to -20°C. An oil separated out and over 24 hours solidified. The solution was decanted and the solid was collected using hexanes to yield 769 mg (84%). mp= 63-7°C. $[\alpha]_D$= -20.4° (c=1.0, MeOH). MS(CI) m/e 398(m+H)$^+$, 241, 213. ^{1}H NMR($CDCl_3$,300MHz) δ 0.88(t,J=7Hz,3H), 0.93(t,J=6Hz,3H), 1.24-1.43(m,8H), 1.51-1.75(m,3H), 1.80-1.90(m,1H), 1.94-2.28(m,3H), 2.32-2.45(m,1H), 3.16-3.37(m,2H), 3.43-3.54(m,2H), 4.0-4.08(m,1H), 4,12-4.2(m,1H), 5.02(dd,J=4,8Hz,1H), 6.96(bs,1H), 7.12(dt,J=1,8Hz,1H), 7.28(dt,J=1,7Hz,1H), 7.48(dd,J=1,8Hz,1H), 7.67(d,J=8Hz,1H), 9.30(s,1H) C,H,N analysis calculated for $C_{24}H_{35}N_3O_2$: C 72.50, H 8.87, N 10.57; found: C 72.55, H 8.91, N 10.49.

Example 104

Methyl 2-(3'-Quinolylcarbonylamino)-2-methylpropionate

Quinoline-3-carboxylic acid (1.12g, 6.5 mmol), methyl α-aminoisobutyrate (1.0g, 6.5 mmol) and TEA (1.8 mL, 1.3 mmol) were dissolved in 50 mL methylene chloride and treated with EDCI (1.2g, 6.5 mmol) overnight. The solvent was evaporated and the residue was extracted as in example 71 to give a white solid, 660 mg, 2.58 mmol (40%). mp= 138-140^{o}C. MS(CI) m/e 273(m+H)$^{+}$. ^{1}H NMR($CDCl_3$,300MHz) δ 1.75(s,6H), 3.82(s,3H), 7.06(s,1H), 7.62(d,J=1,7Hz,1H), 7.81(dt,J=1,7Hz,1H), 7.91(dd,J=1,8Hz,1H), 8.15(d,J=8Hz,1H), 8.58(d,J=2Hz,1H), 9.28(d,J=2Hz,1H).

Example 105

2-(3'-Quinolylcarbonylamino)-2-methylpropionic acid

The product of example 104 (620 mg, 2.42 mmol) was dissolved in 50 mL methanol and treated with 1 N NaOH (2.5 mL, 2.5 mmol). An additional 2.5 mL was added after 1 day. After 2 days, the solvent was evaporated and the residue was dissolved in water and extracted with ethylacetate. The aqueous phase was then acidified and re-extracted with ethylacetate. This second EtOAc layer was dried over $MgSO_4$, filtered and evaporated to yield 406 mg, 1.67 mmol (69%). R_f= 0.3 (80:20:1 $CHCl_3$-CH_3OH-NH_4OH).

Example 106

2-(3'-Quinolylcarbonylamino)-2-methylpropion-di-n-pentyl-amide

The product of example 105 (100 mg, 0.413 mmol), dipentylamine (202 µL, 1.0 mmol) and TEA (59 µL, 0.42

mmol) were dissolved in 15 mL methylene chloride, treated with EDCI (80 mg, 0.42 mmol) and stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ethylacetate and extracted as in example 71. NMR indicated the presence of undesired dehydrated product (oxazolone). MS(CI) m/e 241(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 1.61(s,6H), 7.66(dt,J=1,7Hz,1H), 7.86(dt,J=1,7Hz,1H), 7.94(dd,J=1,8Hz,1H), 8.20(d,J=8Hz,1H), 8.74(d,J=2Hz,1H), 8.98(d,J=2Hz,1H). The crude dehydrated product was redissolved in 25 mL THF and treated with dipentylamine (202 µL, 1.0 mmol). Another 400 mL of dipentylamine was added at 2 and 4 days. After evaporation of the solvent, the residue was purified by chromatography on silica gel eluted with a 4:1 to 1:1 hexane-ethylacetate step gradient to yield 51 mg, 0.13 mmol (32%). mp= 134-5°C. MS(CI) m/e 398(m+H)$^+$, 158. ^{1}H NMR($CDCl_3$,300MHz) δ 0.92(t,J=7Hz,6H), 1.25-1.49(m,12H), 1.90(s,6H), 3.40(bs,4H), 7.61(dt,J=1,7Hz,1H), 7.80(dt,J=1,7Hz,1H), 7.91(dd,J=1,8Hz,1H) 8.15(d,J=8Hz,1H), 8.58(d,J=2Hz,1H), 8.69(s,1H), 9.37(d,J=2Hz,1H). C,H,N analysis calculated for $C_{24}H_{35}N_3O_2$, 0.25 H_2O: C 71.69, H 8.90, N 10.45; found: C 71.65, H 8.74, N 10.39.

Example 107

N-(3'-Quinolylcarbonyl)-R-Lysine-di-n-pentylamide hydrobromide

The product of example 62 (1.61 g, 2.64 mmol) was treated with 15 mL of HBr in HOAc (1.1 N, 16.5 mmol) for 2 hours under an inert atmosphere. The solvent was evaporated and the residue was purified by chromatography

on silica gel eluted with a methylene chloride to 1% ethanol in CH_2Cl_2 step gradient to yield 1.25 g, 2.39 mmol (91%) as a yellow glass. mp= 85-95°C. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 0.85(t,J=7Hz,6H), 1.23-1.83(m,18H), 2.78(t,J=7Hz,2H), 3.06-3.17(m,1H), 3.28-3.44(m,3H), 4.86-4.93(m,1H), 7.57(bs,2H), 7.72(dt,J=1,7Hz,1H), 7.88(dt,J=1,7Hz,1H), 8.10(d,J=8Hz,2H), 8.92(d,J=2Hz,1H), 9.02(d,J=8Hz,1H), 9.32(d,J=2Hz,1H).

Example 108

N^{α}-(3'-Quinolylcarbonyl)-N^{ε}-phenylthiolcarbonyl-R-Lysine dipentylamide

The product of example 107 (20 mg, 0.045 mmol) was treated with carbonyldiimidazole (8.1 mg, 0.05 mmol) in 10 mL methylene chloride at room temperature overnight. Thiophenol (10.3 µL, 0.10 mmol) and 10 mL THF were added and the mixture was heated to 60°C. After 1 day, the reaction was eluted on silica gel with 1% ethanol in methylene chloride to yield an oil. MS(CI) m/e 577(m+H)$^+$, 467, 420. ^{1}H NMR($CDCl_3$,300MHz) δ 0.88-0.96(m,6H), 1.23-1.86(m,18H), 3.12(dt,J=7,13Hz,1H), 3.22-3.44(m,4H), 3.59(dt,J=7,13Hz,1H), 5.0-5.17(m,1H), 5.70(t,J=5Hz,1H), 7.32-7.37(m,3H), 7.47-7.51(m,3H), 7.62(dt,J=1,8Hz,1H), 7.82(dt,J=1,7Hz,1H), 7.91(dd,J=1,8Hz,1H), 8.16(d,J=8Hz,1H), 8.63(d,J=2Hz,1H), 9.37(s,J=2Hz,1H).

Example 109

N-Benzyloxycarbonyl-R-Phenylglycine-(2'-propylpiperidinyl)amide

N-Benzyloxycarbonyl-R-phenylglycine (1.0 g, 3.5 mmol), 2-propylpiperidine (1 mL, 6.64 mmol), HOBt (475 mg, 3.5 mmol) and TEA (490 μL, 3.5 mmol) were dissolved in 25 mL of CH_2Cl_2 and treated with BOPCl (890 mg, 3.5 mmol). Additional TEA (490 μL) and BOPCl(890 mg) were added after 2 days. After 6 days, the solvent was evaporated and the crude reaction was purified by chromatography on silica gel eluted with a 9:1 to 4:1 hexane-ethylacetate step gradient to yield 179 mg, 0.454 mmol (13%). mp= 100-115°C. $[\alpha]_D$= -13.5° (c=1.0, MeOH). MS(CI) m/e 395$(m+H)^+$, 261. ^1H NMR($CDCl_3$,300MHz) δ 0.52(t,J=7Hz,1H), 0.92(t,J=7Hz,2H), 1.18-1.70(m,10H), 2.56-2.67(m,0.33H), 3.01(dd,J=2,13Hz,0.67H), 3.57(bd,J=12Hz,0.67H), 3.80(bs,0.33H), 4.51(bd,J=13Hz,0.33H), 4.78(bs,0.67H), 4.98(d,J=11Hz,1H), 5.12(d,J=11Hz,1H), 5.54(d,J=7Hz,0.67H), 5.58(d,J=7Hz,0.33H), 6.46-6.55(m,1H), 7.28-7.43(m,10H).

Example 110

R-Phenylglycine-(2'-propylpiperidinyl)amide

The product of example 109 (150 mg, 0.38 mmol) was treated with 25 mg of 10% Pd on carbon in 5 mL of methanol under one atmosphere of hydrogen for 24 hours. The catalyst was filtered away and the filtrate was evaporated to yield product.

Example 111

N-(3'-Quinolylcarbonyl)-R-phenylglycine-(2'-propylpiperidinyl)amide

Quinoline-3-carboxylic acid (38.1 mg, 0.22 mmol), the product of example 110 (31 mg, 0.22 mmol) and TEA (31 µL, 0.22 mmol) were dissolved in 4 mL of 1:1 DMF-CH_2Cl_2 and treated with EDCI (42.1 mg, 0.22 mmol) with stirring at room temperature overnight. The solvent was evaporated and the residue was extracted as in example 71. R_f= 0.4 (1:1 hexane-ethylacetate). MS(CI) m/e 416(m+H)$^+$, 261, 154, 128. ^{1}H NMR($CDCl_3$,300MHz) δ 0.55(t,J=7Hz,1H), 0.94(t,J=7Hz,2H), 1.23-1.72(m,10H), 2.71(dt,J=2,13Hz,0.33H), 3.08(dt,J=2,13Hz,0.67H), 3.68(bd,J=13Hz,0.67H), 3.93(bs,0.33H), 4.58(bd,J=13Hz,0.33H), 4.85(bs,0.67H), 6.03(d,J=7Hz,0.67H), 6.07(d,J=7Hz,0.33H), 7.3-7.42(m,3H), 7.52-7.63(m,3H), 7.80(dt,J=1,7Hz,1H), 7.90(d,J=8Hz,1H), 8.14(d,J=8Hz,1H), 8.28(t,J=6Hz,1H), 8.59(d,J=2Hz,1H), 9.34(d,J=2Hz,1H). C,H,N analysis calculated for $C_{26}H_{29}N_3O_2$, 0.5 H_2O: C 73.56, H 7.12, N 9.90; found: C 73.60, H 7.10, N 9.61.

Example 112

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-phenylglycine-(2'-propylpiperidinyl)amide

4,8-Dihydroxyquinoline-2-carboxylic acid (45 mg, 0.22 mmol), the product of example 110 (52 mg, 0.20 mmol) and TEA (31 µL, 0.22 mmol) were dissolved in 4 mL of 1:1 DMF-methylene chloride and treated with EDCI (42 mg, 0.22 mmol) with stirring overnight. The reaction was then

poured into ethylacetate and extracted as in example 71. The resulting residue was purified by chromatography on silica gel eluted with a 1% to 9% ethanol in methylene chloride step gradient. MS(CI) m/e 448$(m+H)^+$, 293. ^1H NMR($DMSO_{d6}$,300MHz) δ 0.71(t,J=7Hz,1H), 0.81-0.90(m,2H), 1.15-1.70(m,10H), 3.07(bt,J=13Hz,0.67H), 3.33(s,H_2O), 3.68(bd,J=12Hz,0.67H), 4.02(bs,0.33H), 4.36(d,J=8Hz,0.33H), 4.68(bs,0.67H), 6.12-6.17(m,1H), 7.09(d,J=7Hz,1H), 7.32-7.56(m,8H), 9.84(d,J=8Hz,0.67H), 10.08(d,J=8Hz,0.33H), 10.23(s,0.67H), 10.24(s,0.33H), 11.73(bs,1H).

Example 113

N^{α}-Benzyloxycarbonyl-R-phenylglycine-(N-benzyl, N-2'-cyanoethyl)amide

N-Benzyloxycarbonyl-R-phenylglycine (285 mg, 1.0 mmol), 3-(benzylamino)propionitrile (391 µL, 2.5 mmol) and TEA (139 µL, 1.0 mmol) were dissolved in 10 mL of CH_2Cl_2 and treated with BOPCl (256 mg, 1.0 mmol). After 1 day, another 139 µL of TEA was added. After 2 days, additional BOPCl (256 mg), amine (391 µL) and DMF (5 mL) were added. After 3 days, the solvents were evaporated and the residue was extracted as in example 71. The crude residue was recrystallized from hexanes-ethylacetate to yield 314 mg, 0.74 mmol (74%). R_f= 0.75 (1:1 hexanes-ethylacetate). mp= 114-150°C. $[\alpha]_D$= -9.4° (c=0.67, 1:1 DMF-MeOH). MS(CI) m/e 428$(m+H)^+$, 445, 384, 375. ^1H NMR($CDCl_3$,300MHz) δ 2.45-2.66(m,2H), 3.33-3.42(m,1H), 3.46-3.52(m,0.5H), 3.66-3.75(m,1H), 4.38(d,J=16Hz,1H), 4.43-4.5(m,0.5H), 4.63(d,J=16Hz,1H), 4.69(s,0.5H), 5.01-5.2(m,3H),

5.59(d,J=7Hz,0.5H), 5.66(d,J=7Hz,1H), 6.88(s,0.5H), 6.18-6.27(m,1.5H), 6.82(bs,0.5H), 6.95(t,J=4Hz,2H), 7.10-7.18(m,2H), 7.28-7.39(m,15H). C,H,N calculated for $C_{26}H_{25}N_3O_3$, 0.1 H_2O: C 72.74, H 5.92, N 9.79; found: C 72.79, H 5.99, N 9.40.

Example 114

R-Phenylglycine-(N-benzyl,N-2'-cyanoethyl)amide

The product of example 113 (225 mg, 0.53 mmol) was dissolved in 25 mL of ethanol and treated with 100 mg of 10% Pd/C at room temperature. After 1.5 hours, the catalyst was filtered and the filtrate was evaporated to yield 158 mg, 0.54 mmol(quantitative). MS(CI) m/e 294$(m+H)^+$, 241.

Example 115

N-(3'-Quinolylcarbonyl)-R-phenylglycine (N-benzyl,N-2'-cyanoethyl)amide

Quinoline-3-carboxylic acid (35 mg, 0.20 mmol) and the product of example 114 (53 mg, 0.18 mmol) were dissolved in 10 mL of methylene chloride and treated with EDCI (38 mg, 0.20 mmol). After 1 day, the solvent was evaporated and the residue was extracted as in example 71 to give 54 mg, 0.12 mmol (67%). $[\alpha]_D = -0.42^\circ$ (c=2.6, $CHCl_3$). mp= 57-63°C. MS(CI) m/e 449$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 1.90-2.02(m,0.25H), 2.27-2.38(m,0.25H), 2.49-2.72(m,1.5H), 3.42(dt,J=7,13Hz,1H), 3.81(dt,J=7,13Hz,1H), 4.46(d,J=16Hz,1H), 4.73(d,J=16Hz,1H), 6.11(d,J=6Hz,0.25H), 6.16(d,J=7Hz,0.75H), 6.98-7.02(m,2H), 7.19-7.22(m,0.5H),

7.30-7.33(m,2.5H), 7.38-7.46(m,3H), 7.53-7.64(m,3H), 7.82(dt,J=1,7H,1H), 7.85-7.94(m,2H), 8.15(d,1H,J=8Hz), 8.61(d,J=1Hz,1H), 9.33(d,J=1Hz,1H). C,H,N analysis calculated for $C_{28}H_{24}N_4O_2$, 0.7 H_2O: C 72.93, H 5.55, N 12.15; found: C 72.86, H 5.58, N 11.77.

Example 116

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-phenylglycine (N-benzyl,N-2'-cyanoethyl)amide

4,8-Dihydroxyquinoline-2-carboxylic acid (41 mg, 0.20 mmol), the product of example 114 (53 mg, 0.18 mmol), and TEA (28 μL, 0.20 mmol) were dissolved in 5 mL of DMF and treated with EDCI (38 mg, 0.20 mmol). Additional TEA (28 μL) and EDCI (38 mg) were added after 2 hours and 1 day. After 2 days HOBt (27 mg, 0.20 mmol) was added to the reaction mixture. After 3 days, the solvent was evaporated and the residue was extracted with 0.1 M citric acid, and water and the organic solution was dried over $MgSO_4$ then filtered and concentrated. The crude product was purified by silica gel chromatography eluted with 1:1 hexanes-ethylacetate to provide 22.6 mg, 0.05 mmol (26%). R_f= 0.4 (1:1 hexane-ethylacetate). mp= 218-222°C. $[\alpha]_D$= -4.8° (c=0.42, MeOH). MS(CI) m/e 481(m+H)$^+$, 428. ^1H NMR(CD_3OD,300MHz) δ 2.47-2.58(m,0.33H), 2.6-2.82(m,2H), 3.33-3.62(m,2.33H), 3.68-3.78(m,0.33H), 3.82-3.91(m,1H), 4.53(d,J=16Hz,1H), 4.62(d,J=14Hz,0.33H), 4.76(d,J=16Hz,1H), 4.87(s,H_2O), 4.92(d,J=5Hz,0.33H), 6.18(s,1H), 7.10(dd,J=1,7Hz,1H), 7.2-7.35(m,7H), 7.39-7.46(m,3H), 7.51-7.60(m,2H), 7.67(dd,J=1,8Hz,1H).

Example 117

N-(3'-Quinolylcarbonyl)-R-Tyrosine-di-n-pentylamide

hydrochloride

hydrochloride

The product of example 80 (1.5 g, 3.0 mmol) was treated with 1.4 N HCl in dioxane (11 mL, 15 mmol) for 10 minutes. The excess reagent was evaporated and the oily residue was triturated with diethylether and filtered to yield 1.3 g, 2.6 mmol (87%) of a pale yellow solid. MS(CI) m/e 476(m+H)$^+$, 458. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 0.84(t,J=7Hz,6H), 1.15-1.62(m,12H), 2.87-3.22(m,3H), 3.29-3.40(m,3H), 5.02(apparent q,J=7Hz,1H), 6.66(d,J=8Hz,2H), 7.11(d,J=8Hz,2H), 7.78(dt,J=1,8Hz,1H), 7.96(dt,J=1,8Hz,1H), 8.17(t,J=7Hz,2H), 9.04(d,J=2Hz,1H), 9.22(d,J=8Hz,1H), 9.33(d,J=2Hz,1H). C,H,N analysis calculated for $C_{29}H_{37}N_3O_3$, 1.3 HCl: C 66.60, H 7.38, N 8.03; found: C 66.43, H 7.38, N 7.99.

Example 118

N-(3'-Quinolylcarbonyl)-R-Histidine-di-n-pentylamide

dihydrochloride

The product of example 50 (800mg, 1.78 mmol) was dissolved in 13 mL of 1.4 N HCl in acetic acid for 10 min and then the volatiles were evaporated to remove excess reagent. The oily residue was dissolved in a small amount of CH_2Cl_2 and the product was precipitated with hexanes. The solid was collected to yield 824 mg, 1.58 mmol (89%). MS(CI) m/e 450(m+H)$^+$. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ

0.74(t,J=7Hz,3H), 0.85(t,J=7Hz,3H), 1.12-1.32(m,8H), 1.41-1.52(m,4H), 3.08-3.43(m,6H), 5.24-5.31(m,1H), 7.45(s,1H), 7.77(dt,J=1,7Hz,1H), 7.94(dt,J=1,7Hz,1H), 8.15(dt,J=1,9Hz,2H), 9.02(s,2H), 9.31-9.33(m,2H), 14.18(s,1H), 14.57(s,1H). C,H,N analysis calculated for $C_{26}H_{35}N_5O_2$, 2.6 HCl: C 57.36, H 6.96, N 12.87; found: C 57.30, H 6.96, N 12.86.

Example 119

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-(4'-hydroxyphenyl)-glycine-di-n-pentylamide

The reaction was performed in a similar manner to that in example 8 utilizing 0.3 g of the compound of example 64, 4',8'-dihydroxyquinoline-2-carboxylic acid (0.2 g), EDCI (0.21 g), HOBt (0.13 g) and NMM (0.22 mL). The product was isolated in 75% yield (0.37 g). MS(CI) m/e 494$(m+H)^+$.
^1H NMR($DMSO_{d6}$,300MHz) δ 0.85(m,6H), 1.1-1.35(m,10H), 1.38-1.45(m,4H), 3.0-3.5(m,4H), 5.95(d,J=9Hz,1H), 6.76(d,J=9Hz,2H), 7.08(d,J=9Hz,1H), 7.23(d,J=9Hz,2H), 7.4(t,J=9Hz,1H), 7.55(m,2H), 9.5(bs,1H), 9.75(d,J=10Hz,1H). C,H,N calculated for $C_{28}H_{35}N_3O_5$, 0.5 H_2O: C 66.91, H 7.22, N 8.36; found: C 66.76, H 7.20, N 8.18.

Example 120

N-Benzyloxycarbonyl-glycine-di-n-pentylamide

The compound was prepared in a manner similar to that in example 1 utilizing N-t-butyloxycarbonylglycine. MS(CI) m/e 349$(m+1)^+$, 305, 241, 215, 184. ^1H

NMR($CDCl_3$,300MHz) δ 7.30-740(m,5H), 5.86(bs,1H), 5.12(bs,2H), 4.0(bd,J=4.5Hz,2H), 3.32(t,J=7.5Hz,2H), 3.15(t,J=7.5Hz,2H), 1.50-1.70(m,4H), 1.20-1.40(m,8H), 0.9(m,6H).

Example 121

N-(2'-Indolylcarbonyl)-glycine-di-n-pentylamide

The product of example 120 was deprotected in a manner similar to that in example 80. The free amine product was then coupled with indole-2-carboxylic acid as in example 4. mp= 98-100°C. MS(EI) m/e 357$(m)^+$, 287, 184. ^1H NMR($CDCl_3$,300MHz) δ 9.27(s,1H), 7.67(d,J=6Hz,1H), 7.45(bd,J=7Hz,2H), 7.29(dt,J=1,6Hz,1H), 7.14(dt,J=1,6Hz,1H), 6.98(s,1H), 4.27(d,J=4Hz,2H), 3.39(bt,J=7Hz,2H), 3.25(bt,J=7Hz,2H), 1.55-1.70(m,4H), 1.25-1.40(m,8H), 0.93(t,J=6Hz,3H), 0.91(t,J=6Hz,3H). C,H,N analysis calculated for $C_{21}H_{31}N_3O_2$, 0.3 H_2O: C 69.51, H 8.78, N 11.58; found: C 69.45, H 8.58, N 11.47.

Example 122

Ethyl N-(t-Butyloxycarbonyl)glycinyl-(N-benzyl)glycinate

N-t-Butyloxycarbonylglycine and ethyl N-benzylglycinate were coupled in a manner similar to that in example 1 to provide product.

Example 123

Ethyl N-(3'Quinolylcarbonyl)glycinyl-(N-benzyl)glycinate

The product of example 122 was deprotected in a manner similar to that in example 2 and then coupled in a manner similar to that in example 3 to provide product. MS(CI) m/e 406(m+H)$^+$, 334, 194. ^{1}H NMR($CDCl_3$,300MHz) δ 9.37(d,J=2Hz,0.33H), 9.35(d,J=2Hz,0.67H), 8.65(bm,1H), 8.18(bd,J=7Hz,1H), 7.94(m,1H), 7.83(m,1H), 7.63(m,1H), 7.43-7.55(m,1H), 7.30-7.40(m,3H), 7.25(m,2H), 4.73(s,0.67H), 4.67(s,1.33H), 4.51(d,J=4Hz,1.33H), 4.33(d,J=4Hz,0.33H), 4.16-4.25(m,2H), 4.13(s,1.33H), 4.00(s,0.67H), 1.28(m,3H).

Example 124

N-(t-Butyloxycarbonyl)-R-homophenylalanine-di-n-pentylamide

The product was prepared in an analogous manner to that in example 1 using t-Butyloxycarbonyl-R-homophenylalanine. MS(CI) m/e 419(m+H)$^+$, 363, 345, 319. ^{1}H NMR($CDCl_3$,300MHz) δ 7.85(m,1H), 7.48(m,1H), 7.18-7.32(m,5H), 5.39(bd,J=9Hz,1H), 4.56(m,1H), 3.48(dt,J=7,14Hz,1H), 3.39(t,J=7Hz,1H), 3.08(m,2H), 2.68(m,2H), 1.88(m,2H), 1.45(s,9H), 1.20-1.35(m,8H), 1.13(m,2H), 0.88(m,6H).

Example 125

N-(3'-Quinolylcarbonyl)-R-homophenylalanine-di-n-pentylamide

The product was prepared in analogous manner to those in examples 2 and 3 utilizing the product of example 124 as the starting material. MS(CI) m/e 474(m+H)$^+$, 369, 319, 305, 289. ^{1}H NMR($CDCl_3$,300MHz) δ 9.32(d,J=2Hz,1H), 8.53(d,J=2Hz,1H), 8.16(bd,J=8Hz,1H), 7.90(dd,J=1,8Hz,1H), 7.82(m,1H), 7.62(m,1H), 7.40(bd,J=8Hz,1H), 7.30(m,4H), 7.20(m,1H), 5.19(m,1H), 3.55-3.70(m,1H), 3.05-3.20(m,3H), 2.78(bt,J=7.5Hz,2H), 2.15(m,2H), 1.50-1.65(m,4H), 1.15-1.35(m,8H), 0.90(m,6H).

Example 126

N-(3'-Quinolylcarbonyl)glycine

Quinoline-3-carboxylic acid and methyl glycinate hydrochloride were coupled in a manner similar to that in example 3. The resulting product was subjected to saponification in methanol with 1 N NaOH. The desired product was extracted with EtOAc from the acidified solution or alternatively allowed to slowly precipitate from the acidified solution. MS(CI) m/e 231(m+H)$^+$, 187. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 12.72(bs,1H), 9.32(d,J=4Hz,1H), 9.11(t,J=6Hz,1H), 8.87(d,J=3Hz,1H), 8.12(t,J=7Hz,2H), 7.89(t,J=7Hz,1H), 7.71(t,J=7Hz,1H), 4.03(bs,2H).

Example 127

N-(3'-Quinolylcarbonyl)glycine-di-n-pentylamide

The product of example 126 and di-n-pentylamine were coupled in a manner similar to that in example 1. The product was isolated by chromatography and solidifies upon concentration. mp= 36-37°C. MS(CI) m/e 370 $(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 9.38(d,J=2Hz,1H), 8.65(d,J=1.8Hz,1H), 8.18(d,J=8.5Hz,1H), 7.93(dd,J=1,8Hz,1H), 7.83(m,1H), 7.64(m,2H), 4.32(d,J=3.7Hz,2H), 3.41(bt,J=8Hz,2H), 3.27(bt,J=8Hz,2H), 1.62(m,4H), 1.30-1.45(m,8H), 0.95(t,J=7Hz,3H), 0.92(t,J=7Hz,3H). C,H,N analysis calculated for $C_{32}H_{31}N_3O_2$: C 71.49, H 8.46, N 11.37; found: C 71.28, H 8.42, N 11.36.

Example 128

N-(3'-Quinolylcarbonyl)glycine-(4-propyl)piperidinylamide

The acid from example 126 and 4-propylpiperdine were coupled as in example 1. mp= 116-117°C. MS(CI) m/e 340 $(m+H)^+$, 279, 254, 201. ^1H NMR($CDCl_3$,300MHz) δ 9.36(d,J=2Hz,1H), 8.63(d,J=2Hz,1H), 8.16(d,J=8.5Hz,1H), 7.93(dd,J=1,8Hz,1H), 7.82(m,1H), 7.60(bs,1H), 7.63(m,1H), 4.61(dt,J=2,13Hz,1H), 4.31(m,2H), 3.79(bd,J=10Hz,1H), 3.07(dt,J=3,13Hz,1H), 2.70(dt,J=3,13Hz,1H), 1.81(bm,2H), 1.55(m,1H), 1.05-1.40(m,6H), 0.92(t,J=7Hz,3H). C,H,N analysis calculated for $C_{20}H_{25}N_3O_2$, 0.1 H_2O: C 70.40, H 7.44, N 12.31; found: C 70.19, H 7.44, N 12.15.

Example 129

N-Benzyloxycarbonyl-R-phenylglycine-di-n-pentylamide

The product was obtained from the coupling of N-Benzyloxycarbonyl-R-phenylglycine and di-n-pentylamine as in example 1. MS(CI) m/e 425(m+H)$^+$, 333, 317, 291. ^{1}H NMR($CDCl_3$,300MHz) δ 7.27-7.45(m,10H), 6.48(bd,J=7.5Hz,1H), 5.53(d,J=7.5Hz,1H), 5.12(d,J=12Hz,1H), 5.01(d,J=12Hz,1H), 3.48(m,1H), 3.18(m,2H), 2.97(m,1H), 1.50(m,4H), 1.10-1.35(m,8H), 0.87(t,J=7.5Hz,3H), 0.84(t,J=7.5Hz,3H).

Example 130

R-Phenylglycine-di-n-pentylamide

The product resulted from the hydrogenolysis of the product of example 129. MS(CI) m/e 291(m+H)$^+$, 158. ^{1}H NMR($CDCl_3$,300MHz) δ 7.25-7.40(m,5H), 4.65(bs,1H), 3.52(m,1H), 3.08-3.22(m,2H), 2.92(m,1H), 2.02(bs,2H), 1.50(m,3H), 1.10-1.35(m,9H), 0.88(t,J=7Hz,3H), 0.85(t,J=7Hz,3H).

Example 131

N-(3'Quinolylcarbonyl)-R-phenylglycine-di-n-pentylamide

The product of example 130 was coupled in a similar manner to that in example 3 to provide product. MS(CI) m/e 446(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 9.33(d,J=2Hz,1H), 8.58(d,J=2Hz,1H), 8.13(bt,J=8Hz,2H), 7.88(bd,J=8Hz,1H), 7.79(m,1H), 7.62(m,1H), 7.55(m,2H), 7.32-7.42(m,3H), 6.03(d,J=6Hz,1H), 3.55(m,3H), 1.15-1.40(m,9H), 0.90(t,J=7Hz,3H), 0.86(t,J=7Hz,3H).

Example 132

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-R-Phenylglycine-di-n-pentylamide

The product of example 130 was coupled in a similar manner to that in example 8 to provide the title compound. mp= 89-91°C. MS(CI) m/e 478(m+H)$^{+}$, 293, 190, 177. ^{1}H NMR(DMSO$_{d6}$,300MHz) δ 9.91(bd,J=8Hz,1H), 7.55(m,2H), 7.35-7.45(m,7H), 7.08(dd,J=1,7.5Hz,1H), 6.11(bd,J=8Hz,1H), 3.05-3.30(m,4H), 1.60(m,1H), 1.48(m,2H), 1.13-1.35(m,9H), 0.85(t,J=7Hz,3H), 0.78(t,J=7Hz,3H). C,H,N analysis calculated for $C_{28}H_{35}N_3O_4$, 0.3 H_2O: C 69.63, H 7.43, N 8.70; found: C 69.61, H 7.40, N 8.65.

Example 133

N-(3'-Chlorophenylaminocarbonyl)-R-phenylglycine-di-n-pentylamide

The product of example 130 was reacted with 3-chlorophenylisocyanate to provide the title compound. MS(CI) m/e 444(m+H)$^{+}$, 425, 317, 291, 259, 242. ^{1}H NMR(CDCl$_3$,300MHz) δ 7.95(bs,1H), 7.42(m,1H), 7.22-7.34(m,5H), 7.13(d,J=7.5Hz,1H), 7.08(m,2H), 6.89(m,1H), 5.92(d,J=8Hz,1H), 3.50(m,1H), 3.00-3.30(m,4H), 1.43-1.63(m,3H), 1.10-1.30(m,8H), 0.84(t,J=7Hz,3H), 0.78(t,J=7Hz,3H).

Example 134

N-(3'-Methylphenylaminocarbonyl)-R-phenylglycine-di-n-pentylamide

The product of example 130 was reacted with 3-methylphenylisocyanate to provide the title compound. MS(CI) m/e 424 $(m+H)^+$, 374, 317, 291, 276, 239, 228. ^1H NMR($CDCl_3$,300MHz) δ 7.27-7.48(m,5H), 7.18(m,1H), 7.12(d,J=8Hz,1H), 7.06(m,2H), 6.82(bd,J=8Hz,1H), 6.77(bd,J=8Hz,1H), 5.87(d,J=8Hz,1H), 3.51(m,1H), 3.20(m,2H), 3.04(m,1H), 2.28(s,3H), 1.50(bm,4H), 1.10-1.30(m,8H), 0.84(t,J=7Hz,3H), 0.82(t,J=7Hz,3H).

Example 135

N-(5'-Fluoroindolylcarbonyl)-R-phenylglycine-di-n-pentylamide

The product of example 130 was reacted with 5-fluoroindole-2-carboxylic acid in a manner similar to that in example 4 to provide the desired product. mp= 94-6°C. MS(CI) m/e 452 $(m+H)^+$, 276, 267, 184. ^1H NMR($CDCl_3$,300MHz) δ 9.36(bs,1H), 7.96(d,J=7Hz,1H), 7.50(m,2H), 7.30-7.40(m,3H), 7.36(s,1H), 7.33(m,1H), 6.98(dt,J=2.5,9Hz,1H), 6.91(m,1H), 5.94(d,J=7Hz,1H), 3.53(m,1H), 3.13-3.30(m,2H), 3.04(m,1H), 1.45-1.65(m,4H), 1.10-1.40(m,8H), 0.89(t,J=7Hz,3H), 0.85(t,J=7Hz,3H). C,H,N analysis calculated for $C_{27}H_{34}FN_3O_2$: C 71.81, H 7.59, N 9.31; found: C 71.53, H 7.50, N 9.30.

Example 136

N-(5'-Chloroindolylcarbonyl)-R-phenylglycine-di-n-pentylamide

The product of example 130 was reacted with 5-Chloroindole-2-carboxylic acid in a manner similar to that in example 4 to provide the title compound. MS(CI) m/e 468(m+H)$^+$, 434, 302, 276, 212. ^{1}H NMR($CDCl_3$,300MHz) δ 9.36(bs,1H), 7.97(d,J=7Hz,1H), 7.59(m,1H), 7.50(m,2H), 7.35(m,3H), 7.22(m,2H), 6.89(m,1H), 5.94(d,J=7Hz,1H), 3.53(m,1H), 3.15-3.30(m,2H), 3.04(m,1H), 1.45-1.60(m,4H), 1.10-1.40(m,8H), 0,89(t,J=7Hz,3H), 0.85(t,J=7Hz,3H). C,H,N analysis calculated for $C_{27}H_{34}ClN_3O_2$: C 69.29, H 7.32, N 8.98; found: C 69.44, H 7.36, N 8.95.

Example 137

N-(2'-Quinolylcarbonyl)-R-Phenylglycine-di-n-pentylamide

The product of example 130 was coupled in a similar manner to that in example 5 to provide the desired compound. mp= 116-7^{o}C. MS(CI) m/e 446(m+H)$^+$, 289, 277, 261, 246. ^{1}H NMR($CDCl_3$,300MHz) δ 9.62(d,J=8Hz,1H), 8.24(bs,2H), 8.17(d,J=8Hz,1H), 7.83(d,J=8Hz,1H), 7.74(m,1H), 7.59(m,3H), 7.30-7.40(m,3H), 6.06(d,J=8Hz,1H), 3.61(m,1H), 3.32(m,1H), 3.0-3.20(m,2H), 1.50-1.65(m,4H), 1.15-1.40(m,8H), 0.89(t,J=7Hz,3H), 0.87(t,J=7Hz,3H). C,H,N analysis calculated for $C_{28}H_{35}N_3O_2$: C 75.47, H 7.92, N 9.43; found: C 75.45, H 7.91, N 9.43.

Example 138

N'-(t-Butyloxycarbonyl)-1-amino-cyclohexane-(di-n-pentyl)carboxamide

The product was prepared as in example 1 from di-n-pentylamine and N'-t-Butyloxycarbonyl-1-aminocyclohexane carboxylic acid. MS(CI) m/e 383$(m+H)^+$. ^1H NMR($CDCl_3$,300MHz) δ 4.70(bs,1H), 3.20-3.50(m,4H), 1.85-2.0(m,4H), 1.45-1.70(m,8H), 1.42(bs,9H), 1.20-1.40(m,10H), 0.92(bt,J=7Hz,6H).

Example 139

N'-(3'-Quinolylcarbonyl)-1-amino-cyclohexane-(di-n-pentyl)carboxamide

The desired product was prepared via deprotection of the product of example 138 (in a manner similar to that in example 2) and coupling with quinoline-3-carboxylic acid as in example 3. mp= 136-137°C.

Example 140

N'-(t-Butyloxycarbonyl)-1-amino-cyclohexane(N-pentyl)carboxamide

The product was prepared via coupling of N'-t-Butyloxycarbonyl-1-aminocyclohexane carboxylic acid and pentylamine as in example 1. MS(CI) m/e 313$(m+H)^+$, 257, 239, 213, 198. ^1H NMR($CDCl_3$,300MHz) δ 6.70(s,1H), 4.52(bs,1H), 3.23(m,2H), 1.80-2.05(m,4H), 1.65(m,4H), 1.44(s,9H), 1.25-1.38(m,8H), 0.88(t,J=7Hz,3H).

Example 141

N'-(3'-Quinolylcarbonyl)-1-amino-cyclohexane-(N-pentyl)carboxamide

The product was obtained in a similar manner to that in example 139 using the product of example 140 as the starting material. MS(CI) m/e 368(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 9.38(d,J=2Hz,1H), 8.58(d,J=2Hz,1H), 8.18(d,J=8Hz,1H), 7.94(bd,J=8Hz,1H), 7.83(m,1H), 7.65(m,1H), 7.12(bs,1H), 6.27(bs,1H), 3.38(m,2H), 2.34(m,2H), 2.03(m,2H), 1.65-1.80(m,4H), 1.50-1.60(m,4H), 1.25-1.40(m,4H), 0.88(t,J=7Hz,3H). C,H,N analysis calculated for $C_{22}H_{29}N_3O_2$: C 71.91, H 7.95, N 11.43; found: C 71.73, H 7.95, N 11.33.

Example 142

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)glycine-di-n-pentylamide

The product of example 120 was deprotected in a manner similar to that in example 80 and the resulting amine was then coupled in a manner similar to that in example 8 to yield the title compound. mp= 158.5-159.5^{o}C. MS(FAB) m/e 402(m+H)$^+$, 386, 245, 217. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 9.90(bs,1H), 9.80(bs,1H), 7.55(bt,J=8Hz,1H), 7.52(bs,1H), 7.42(m,1H), 7.11(bd,J=8Hz,1H), 4.20(bd,J=6Hz,2H), 3.36(bs,H_2O), 3.20 - 3.33(m,4H), 1.58(m,2H), 1.48(m,2H), 1.20-1.33(m,8H), 0.85(m,6H). C,H,N analysis calculated for $C_{22}H_{31}N_3O_4$, H_2O: C 62.99, H 7.93, N 10.02; found: C 63.12, H 8.02, N 10.01.

Example 143

N-(2'-Naphthoyl)glycine-di-n-pentylamide

The product of example 120 was deprotected in a manner similar to that in example 80 and the resulting amine was then coupled in a manner similar to that in example 17 to yield the title compound. MS(CI) m/e 369(m+H)$^+$, 200, 184, 172. ^{1}H NMR($CDCl_3$,300MHz) δ 8.38(s,1H), 7.85-7.95(m,4H), 7.50-7.60(m,3H), 4.30(d,J=4Hz,2H), 3.40(t,J=7.5Hz,2H), 3.26(t,J=7.5Hz,2H), 1.60(m,4H), 1.25-1.45(m,8H), 0.94(t,J=7Hz,3H), 0.92(t,J=7Hz,3H). C,H,N analysis calculated for $C_{23}H_{32}N_2O_2$: C 74.96, H 8.75, N 7.68; found: C 74.44, H 8.75, N 7.55.

Example 144

N-(6'-Hydroxy-2'-naphthoyl)glycine-di-n-pentylamide

The product of example 120 was deprotected in a manner similar to that in example 80 and the resulting amine was then coupled with 6-hydroxy-2-naphthoic acid in a manner similar to that in example 17 to yield the title compound. MS(CI) m/e 385(m+H)$^+$, 228, 200, 184. ^{1}H NMR($DMSO_{d6}$,300MHz) δ 8.58(bt,J=6Hz,1H), 8.36(bs,1H), 7.86(m,2H), 7.63(d,J=8Hz,1H), 7.15(m,2H), 4.14(d,J=5Hz,2H), 3.20-3.35(m,4H), 1.60(m,2H), 1.45(m,2H), 1.20-1.35(m,8H), 0.89(t,J=7Hz,3H), 0.86(t,J=7Hz,3H). C,H,N analysis calculated for $C_{23}H_{32}N_2O_3$: C 71.84, H 8.39, N 7.29; found: C 71.73, H 8.36, N 7.21.

Example 145

N-(3'-Methylphenylaminocarbonyl)glycine-di-n-pentylamide

The product of example 120 was deprotected in a manner similar to that in example 80 and the resulting amine was then coupled with 3-methylphenylisocyanate to yield the title compound. mp= 66-7°C. MS (CI) m/e 348(m+H)$^+$, 241, 215, 200, 184. ^{1}H NMR($CDCl_3$,300MHz) δ 7.08-7.20(m,3H), 7.03(bs,1H), 6.86(bd,J=7Hz,1H), 6.21(bs,1H), 4.13(bs,2H), 3.32(bt,J=7.5Hz,2H), 3.21(bt,J=7.5Hz,2H), 2.30(s,3H), 1.45-1.65(m,4H), 1.20-1.40(m,8H), 0.92(t,J=7Hz,3H), 0.86(t,J=7Hz,3H). C,H,N analysis calculated for $C_{20}H_{33}N_3O_2$:
C 69.13, H 9.57, N 12.09; found: C 68.99, H 9.56, N 12.04.

Example 146

N-(2'-Chlorophenylaminocarbonyl)-(2R,3S)-(O-benzyl)Threonine-di-n-pentylamide

The reaction was performed in a similar manner as in the example above utilizing 0.35 g of the hydrochloride salt of example 30, 2-chlorophenylisocyanate (0.16 g), and TEA (0.135 mL). The product was purified using chloroform and methanol as the elutant mixture. The oily product was isolated in 83% yield (0.42 g). $[\alpha]_D$= +21.8° (c=0.11, MeOH). MS(CI) m/e 502(m+H)$^+$. ^{1}H NMR($CDCl_3$,300MHz) δ 0.85(m,6H), 1.23(m,11H), 1.43-1.65(m,4H), 3.0-3.21(m,2H), 3.55(m,2H), 3.33(m,1H), 4.57(d,J=15Hz,1H), 4.63(d,J=15Hz,1H), 4.98(m,1H), 6.48(d,J=9Hz,1H), 6.95(t,J=7Hz,1H), 7.2(m,2H), 7.3(m,6H), 8.11(d,J=9Hz,1H).

C,H,N analysis calculated for $C_{28}H_{40}ClN_3O_3$, 0.3 $CHCl_3$: C 63.19, H 7.55, N 7.81; found: C 63.21, H 7.34, N 7.82.

Example 147

N-(4',8'-Dihydroxy-2'-quinolylcarbonyl)-(2R,3S)-(O-benzyl)-Threonine-di-n-pentylamide

The reaction was performed in a similar manner as in example 8 utilizing 0.35 g of the hydrochloride salt of example 30 4,8-dihydroxyquinoline-2-carboxylic acid (0.21 g), EDCI (0.22 g), HOBt (0.14 g), and NMM (0.22 g). The oily product was isolated in 60% yield (0.32 g). $[\alpha]_D$= +8.0° (c=0.125, MeOH). MS(CI) m/e 536(m+H)$^+$. ^1H NMR($DMSO_{d6}$,300MHz) δ 0.82(m,6H), 1.15-1.3(m,11H), 1.4-1.6(m,4H), 3.2-3.65(m,4H), 4.08(m,1H), 4.52(d,J=12Hz,1H), 4.63(d,J=12Hz,1H), 4.98(t,J=9Hz,1H), 7.12(m,5H) 7.42(t,J=9Hz,1H), 7.55(m,2H), 9.8(d,J=9Hz,1H), 10.4(bs,1H), 11.72(bs,2H). C,H,N analysis calculated for $C_{31}H_{41}N_3O_5$, H_2O: C 67.25, H 7.83, N 7.59; found: C 67.19, H 7.60, N 7.38.

Example 148

Methyl Boc-R-Methionine-S-(p-hydroxy)-phenylglycinate

Boc-R-methionine (250 mg, 1 mmol) , methyl p-hydroxyphenylglycinate hydrochloride (217 mg, 1 mmol) and triethylamine (139 µL, 1 mmol) were combined in 10 mL of dichloromethane at 0°C and treated with BOPCl (254 mg, 1mmol). Additional BOPCl (254 mg) and TEA (134 µL) were added after one day. After two days, the reaction mixture was poured into EtOAc and extracted successively with 0.1% citric acid, 0.1 M $NaHCO_3$ and water. The solution was

then dried over $MgSO_4$, filtered and evaporated to yield 288 mg, 0.7 mmol (70%). Rf = 0.56 (1:1 hexanes - EtOAc) mp = 158^{o}C (dec). MS(CI) m/e 413(m+H)$^{+}$, 357, 313. ^{1}HNMR($CDCl_3$,300MHz) d 1.43(s,9H), 3.72(s,3H), 6.73(d,J=8Hz,2H), 7.17(d,J=8Hz,2H), 7.33(bs,1H).

Example 149

Methyl R-Methionine-S-(p-hydroxy)-phenylglycinate hydrochloride

The product of the example 148 (250 mg, 0.6 mmol) was treated with 5 mL of 4 N HCl in dioxane at room temperature under a nitrogen atmosphere. After 30 minutes, the excess reagent was evaporated to yield quantitatively the product.

Example 150

Methyl N-(3'-Quinolylcarbonyl)-R-Methionine-S-(p-hydroxy)-phenylglycinate

The hydrochloride salt of example 149 (50 mg, 0.14 mmol), 3-quinoline carboxylic acid (26 mg, 0.15 mmol) and TEA (21 µL, 0.15 mmol) were dissolved into 5 mL methylenechloride and treated with EDCI (29 mg, 0.15 mmol) for 4 hours. The reaction was poured into EtOAc and extracted with 0.1% citric acid and water followed by drying over MgSO4. The resultant filtrate was concentrated and chromatographed over silica gel eluting with a 2:1 to 1:2 hexane - EtOAc gradient to yield 29 mg, 0.06 mmol (44%). MS(CI) m/e 468(m+H)$^{+}$, 393, 287. ^{1}HNMR($CDCl_3$,300MHz) δ 2.04(s,3H), 2.12-2.20(m,2H), 2.42-

2.52(m,1H), 2.57-2.67(m,1H), 3.65(s,3H), 5.05(q,J=7Hz,1H), 5.41(d,J=6Hz,1H), 6.77(d,J=8Hz,2H), 7.16(d,J=8Hz,2H), 7.59(dt,J=1,7Hz,1H), 7.73-7.82(m,3H), 7.83(d,J=8Hz,1H), 8.12(d,J=8Hz,1H), 8.61(d,J=2Hz,1H), 9.30(d,J=2Hz,1H). C,H,N analysis calculated for $C_{24}H_{25}N_3O_5S$ 0.5 H_2O: C 60.49, H 5.60, N 8.81; found: C 60.64, H 5.63, N 8.35.

Example 151

N-(3'-Quinolylcarbonyl)-R-Serine-di-n-pentylamide

BTFA (trifluoroacetoxyboronate) 0.154 g, 0.4 mmol was added to the product of example 27 (71 mg, 0.145 mol) dissolved in 2 mL of methylene chloride. Another mL of methylene chloride was added and the reaction was monitored by tlc. After 20 minutes of stirring at ambient temperature, the starting material was consumed and the solvents with methanol were evaporated under vacuum. This evaporation sequence using methanol was repeated several times . The residue was separated by chromatography using EtoAc-hexane (1:1) as the elutants. An oily product was isolated in 69% yield (40 mg). MS(CI) m/e 400 $(m+H)^+$. ^{1}HNMR(CD_3OD,300MHz) δ 0.94 (m,6H), 1.26-1.44 (m,8H), 1.54-1.64(m,2H), 1.68-1.86(m,3H), 3.25-3.35(m,1H), 3.43-3.62(m,3H), 3.82-3.96(m,2H), 5.22(t,J=6Hz,1H), 7.73(t,J=6Hz,1H), 7.91(t,J=6Hz,1H), 8.07(d,J=9Hz,1H), 8.12(d,J=9Hz,1H), 8.9(s,1H), 9.28(s,1H).

Example 152

N-(8'-Hydroxy-2-quinolylcarbonyl)-glycine-di-n-pentylamide

Similar to example 121, the product of example 120 was deprotected and coupled to 8-hydroxy-2-quinolinic carboxylic acid in a standard fashion utilizing EDCI etc. to provide the product. MS(CI) m/e 386 $(m+H)^+$. ^{1}HNMR($CDCl_3$,300MHz) δ 8.96(bs,1H), 8.23(s,2H), 8.02(s,1H), 7.53(t,J=7.5Hz,1H), 7.36(dd,J=1,7.5Hz,1H), 7.23(dd,J=1,7.5Hz,1H), 4.34(d,J=5Hz,2H), 3.42(bt,J=8hz,2H), 3.28(bt,J=8Hz,2H), 1.55-1.70(m,4H), 1.25-1.40(m,8H), 0.93(apparent q,6H). C,H,N analysis calculated for $C_{22}H_{31}N_3O_3$ 0.2 H_2O: C 67.91, H 8.13, N 10.80; found: C 67.90, H 8.14, N 10.69.

Example 153

N-Methyl-N-(3'Quinolylcarbonyl)-glycine-di-n-pentylamide

The product of example 127 was methylated using bistrimethylsilylamide and methyl iodide in THF at -78°C warming to ambient temperature to provide product after standard workup and purification. MS(DCI) m/e 384$(m+H)^+$.

Example 154

N-(3'-Iodo-2'-indolylcarbonyl)-glycine-di-n-pentylamide

The product of example 121 was iodinated with N-iodosuccinimide to provide product after chromatographic purification. MS(DCI) m/e 484$(m+H)^+$. C,H,N analysis calculated for $C_{21}H_{30}IN_3O_2$: C 52.18, H 6.25, N 8.69; found: C 52.04, H 6.21, N 8.49.

Example 155

N-(2'-Indolylcarbonyl)-R-Alanine-di-n-pentylamide

In a similar fashion to examples 57 and 58 the product was prepared from the corresponding R-alanyl-di-n-pentylamide hydrochloride and 3-quinoline carboxylic acid to yield product. MS(CI) m/e 372 $(m+H)^+$. C,H,N analysis calculated for titled product: C 71.1, H 8.95, N 11.31; found: C 70.76, H 9.03, N 11.17.

The ability of the compounds of Formula I to interact with CCK receptors and to antagonize CCK can be demonstrated *in vitro* using the following protocols.

Pharmacological Methods

CCK_8 [Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH2] was purchased from Peptide International (Louisville,KY) or Cambridge Research Biochemicals (Atlantic Beach, NY) EGTA, HEPES and BSA were purchased from Sigma Chemical Co. (St. Louis, MO). [^{125}I]BH-CCK_8 (specific activity, 2200 Ci/mmol) and Aquasol-2 scintillation cocktail were obtained from New England Nuclear (Boston, MA). Bestatin and phosphoramidon were purchased from Peptide International. Male guinea pigs, 250 to 325 g, were obtained from Scientific Small Animal Laboratory and Farm (Arlington Heights, IL).

Protocol for Radioligand Binding Experiments

1. Guinea Pig Cerebral Cortical and Pancreatic Membrane Preparations

Cortical and pancreatic membranes were prepared as described (Lin and Miller; J. Pharmacol. Exp. Ther. 232, 775-780, 1985). In brief, cortex and pancreas were removed and rinsed with ice-cold saline. Visible fat and connective tissues were removed from the pancreas. Tissues were weighed and homogenized separately in approximately 25 mL of ice-cold 50 mM Tris-HCl buffer, pH 7.4 at 4°C, with a Brinkman Poloytron for 30 sec, setting 7. The homogenates were centrifuged for 10 min at 1075 x g and pellets discarded. The supernatants were saved and centrifuged at 38,730 x g for 20 min. The resultant pellets were rehomogenized in 25 mL of 50 mM Tris-HCl buffer with Teflon-glass homogenizer, 5 up and down strokes. The homogenates were centrifuged again at 38,730 x g for 20 min. Pellets were then resuspended in 20 mM HEPES, containing 1 mM EGTA, 118 mM NaCl, 4.7 mM KCl, 5 mM $MgCl_2$, 100 μM bestatin, 3 μM phosphoramidon, pH 7.4 at 22°C, with a Teflon-glass homogenizer, 15 up and down strokes. Resuspension volume was 15-18 mL per gram of original wet weight for the cortex and 60 mL per gram for the pancreas.

2. Incubation Conditions

[^{125}I]Bolton-Hunter CCK_8 ([^{125}I]BH-CCK_8), and the test compounds were diluted with HEPES-EGTA-salt buffer (see above) containing 0.5% bovine serum albumin (BSA). To 1 mL Skatron polystyrene tubes were added 25 µL of [^{125}I]BH-CCK_8, and 200µL of membrane suspension. The final BSA concentration was 0.1%. The cortical tissues were incubated at 30°C for 150 min and pancreatic tissues were incubated at 37°C for 30 min. Incubations were terminated by filtration using Skatron Cell Harvester and SS32 microfiber filter mats. The specific binding of [^{125}I]BH-CCK_8, defined as the difference between binding in the absence and presence of 1 µM CCK_8, was 85-90% of total binding in cortex and 90-95% in pancreas. IC_{50}'s were determined from the Hill analysis. The results of these binding assays are shown in Table 1.

Protocol for Amylase Release

This assay was performed using the modified protocol of Lin et al., J. Pharmacol. Exp. Ther. 236, 729-734, 1986.

1. Guinea Pig Acini Preparation

Guinea pig ocean were prepared by the method of Bruzzone et al. (Biochem. J. 226, 621-624, 1985) as follows. The pancreas was dissected and connective tissues and blood vessels were removed. The pancreas was cut into small pieces (2 mm) by a seizure and placed in a

15 mL conical plastic tube containing 2.5 mL of Krebs-Ringer HEPES (KRH) buffer plus 400 units per mL of collagenase. The composition of the KRH buffer was: HEPES, 12.5 mM; NaCl, 118 mM; KCl, 4.8 mM; $CaCl_2$, 1 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 5 mM; glucose, 10 mM at pH 7.4. The buffer was supplemented with 1% MEM vitamins, 1% MEM amino acids and 0.001% aprotinin. The tube was shaken by hand until the suspension appeared homogeneous, usually 5-6 min. Five mL of the KRH, without collagenase and with 0.1% BSA, was added and the tube was centrifuged at 50 x g for 35 sec. The supernatant was discarded and 6 mL of the KRH was added to the cell pellet. Cells were triturated by a glass pipette and centrifuged at 50 x g for 35 sec. This wash procedure was repeated once. The cell pellet from the last centrifugation step was then resuspended in 15 mL of KRH containing 0.1% BSA. The contents were filtered through a dual nylon mesh, size 275 and 75 μM. The filtrate, containing the acini, was centrifuged at 50 x g for 3 min. The acini were then resuspended in 5 mL of KRH-BSA buffer for 30 min at 37°C, under 100% oxygen atmosphere (O_2), with a change of fresh buffer at 15 min.

2. <u>Amylase Assay</u>

After the 30 min incubation time, the acini were resuspended in 100 volumes of KRH-BSA buffer, containing 3 μM phosphoramidon and 100 μM bestatin. While stirring, 400 μL of acini were added to 1.5 mL microcentrifuge tubes

containing 50 µL of CCK_8, buffer, or test compounds. The final assay volume was 500 µL. Tubes were vortexed and placed in a 37°C water bath, under 100% O_2, for 30 min. Afterward, tubes were centrifuged at 10,000 g for 1 min. Amylase activity in the supernatant and the cell pellet were separately determined after appropriate dilutions in 0.1% Triton X-100, 10 mM NaH_2PO_4, pH 7.4 by Abbott Amylase A-gent test using the Abbott Bichromatic Analyzer 200. The reference concentration for CCK_8 in determining the IC_{50}'s of the compounds of Formula I was 3×10^{-10}M. The results of this assay are shown in Table 2.

In Vitro Results

The preferred compounds of Formula I are those which inhibited specific $[^{125}I]$-BH-CCK_8 binding in a concentration dependent manner. Analysis of $[^{125}I]$-BH-CCK_8 receptor binding in the absence and presence of the compounds of formula I indicated the compounds of formula I inhibited specific $[^{125}I]$-BH-CCK_8 receptor binding. The IC_{50} values of the compounds of Formula I are presented in Table 1.

TABLE 1

$[^{125}I]$-BH-CCK_8 Binding

Compound of Example	IC_{50} (nM) Pancreas	Cortex
3	40	17,000
4	100	>10,000
5	27	>10,000
7	290	>10,000
8	12	<10,000
13	190	1-10,000
17	200	~100,000
23	87	~10,000
24	170	>10,000
27	140	7200
31	73	~10,000
32	23	≥10,000
33	30	~10,000
34	9	>10,000
37	210	~10,000
43	48	1400
47	320	~10,000
50	19	2400
53	24	~10,000
56	530	>10,000
62	140	5200
65	41	<10,000
66	150	1-10,000

70	260	~10,000
73	180	>10,000
74	70	~10,000
75	160	>10,000
76	92	>10,000
80	37	~10,000
81	120	5300
82a	250	>30,000
87	29	≥10,000
91	120	3000
93	145	~10,000
99	56	~10,000
100	63	~10,000
117	74	28,000
118	42	3,300
119	110	6,200
125	160	~10,000
131	9.3	1600
132	3.1	1700
133	210	~10,000
135	69	6000
142	160	>10,000
143	130	
145	100	
147	86	2,900
150	980	>10,000
151	51	
152	520	>10,000
155	230	<10,000

The results herein also indicate that compounds of the invention possess selectivity for the pancreatic (type A) CCK receptors.

TABLE 2

Compound of Example	Inhibition of CCK_8-induced Amylase Release IC_{50} (nM)
3	290
4	<100,000
8	<100,000
17	<30,000
31	<100,000
32	<1000
34	<100,000
43	140
50	<100,000
54	~100,000
65	<100,000
74	<100,000
80	<10,000
81	<10,000

91	<10,000
99	<10,000
131	<100,000
132	<100,000
141	<30,000
151	<10,000

These results indicate that compounds of the invention are CCK antagonists.

<u>In Vivo Results</u>

The ability of the compounds of Formula I to interact with CCK receptors and to antagonize CCK *in vivo* can be demonstrated using the following protocols.

<u>Inhibition of CCK Induced Gastric Emptying</u>

Three fasted mice were dosed (p.o.) with the test compound. CCK_8 (80 µg/kg s.c.) was administered within 60 minutes and charcoal meal (0.1 mL of 10% suspension) was given orally 5 minutes later. The animals were sacrificed within an additional 5 minutes.

Gastric emptying, defined as the presence of charcoal within the intestine beyond the pyloric sphincter, is inhibited by CCK_8. Gastric emptying observed in 2 or 3 mice (greater than 1) indicates antagonism of CCK_8.

Compound of example	Dose (p.o.)	Number of mice with Gastric Emptying
118	100 mg/kg	2

Measurement of Plasma Insulin Level Following Treatment with CCK_8 and a Compound of Formula I

The ability of the compounds of Formula I to antagonize CCK induced hyperinsulinemia can be demonstrated in vivo using the following protocol.

Male mice, 20-30 g, were used in all experiments. The animals were fed with laboratory lab chow and water ad libitum. The compound of Formula I (1-100 mg/kg in 0.2 mL of 0.9% saline) was administered i.p. Ten minutes later CCK_8 (0.2 to 200 nmole/kg in 0.2 mL of 0.9% saline) or saline was injected into the tail vein. Two minutes later the animals were sacrificed and blood was collected into 1.5 mL heparinized polypropylene tubes. The tubes were centrifuged at 10,000 x g for 2 minutes. Insulin levels were determined in the supernatant (plasma) by an RIA method using kits from Radioassay Systems Laboratory (Carson, CA.) or Novo Biolabs (MA.).

Antagonism of CCK Mediated Behavioral Effect in Mice with Compounds of Formula I

Male Swiss CD-1 mice (Charles River) (22-27 g) are provided ample food (Purina Lab Chow) and water until the time of their injection with the test compounds.

ICV injections were given by a free-hand method similar to that previously described (Haley and McCormick, Br. J. Pharmacol. Chemother. 12, 12-15 1957). The animals were placed on a slightly elevated metal grid and restrained by the thumb and forefinger at the level of the shoulders, thus immobilizing their heads. Injections were made with a 30 gauge needle with a "stop" consisting of a piece of tygon tubing to limit penetration of the needle to about 4.5 mm below the surface of the skin. The needle was inserted perpendicular to the skull at a midline point equidistant from the eye and an equal distance posterior from the level of the eyes such that the injection site and the two eyes form an equilateral triangle. The injection volume (5 μL) was expelled smoothly over a period of approximately 1 second.

Immediately after the injections the mice were placed in their cages and allowed a 15 minute recovery period prior to the beginning of the behavioral observations.

For the behavioral observations, the mice were placed in clear plastic cages. Each cage measured 19 x 26 x 15 centimeters and contained a 60-tube polypropylene test tube rack (NALGENE #5970-0020) placed on end in the center of the cage to enhance exploratory activity. Observations were made every 30 seconds for a period of 30 minutes. Behavior was compared between drug and CCK_8 treated mice; CCK_8 treated mice; and mice treated with an equal volume of carrier (usually 0.9% saline or 5% dimethylsulfoxide in water). Locomotion as reported here consisted of either floor locomotion or active climbing on the rack. Differences among groups were analyzed by Newman-Kewels

analysis and a probability level of $p< 0.05$ was accepted as significant. Each group tested consisted of 10 animals. The results of this test indicate that compounds of Formula I are antagonists of CCK in vivo. Minimally effective doses (MED) are defined as that dose at which a statistically significant reversal of CCK-induced inactivity was observed when the test compound of formula I and CCK_8 were coadministered.

Compound of Example	Dose of CCK_8	MED
43	3 nmol	3 nmol

The compounds of Formula I antagonize CCK which makes the compounds useful in the treatment and prevention of disease states in mammals (especially humans) wherein CCK or gastrin may be involved, for example, gastrointestinal disorders such as irritable bowel syndrome, ulcers, excess pancreatic or gastric secretion, hyperinsulinemia, acute pancreatitis, GI cancers (especially cancers of the gall bladder and pancreas), motility disorders, pain (potentiation of opiate analgesia), central nervous system disorders caused by CCK's interaction with dopamine such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis, including schizophrenia, or Gilles de la Tourette Syndrome; disorders of the appetite regulatory

systems, bulimia, Zollinger-Ellison syndrome, and central G cell hyperplasia, and the treatment of substance abuse.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptonate, glycerphosphate, hemisulfate, heptonate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates, long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, arylalkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt forming inorganic or organic

acid or base in a suitable solvent or various combinations of solvents.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid and phosphoric acid and such organic acids such as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium, or magnesium or with organic bases.

The pharmaceutically acceptable salts of the acid of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, cyclohexylamine, dicyclohexylamine, triethylamine, piperidine, pyrrolidine, benzylamine, and the like, or a quaterary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

When a compound of Formula I is used as an antagonist of CCK or gastrin in a human subject, the total daily dose administered in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg a day and more usually 1 to 1000 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form

will vary depending upon the host treated, the particular treatment and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-

or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsion, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The present agents can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-

lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the compounds of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

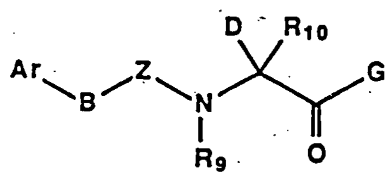
Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Vol. XIV, Academic Press, New York, N. Y. 1976, p.33 et seq.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. A compound of the formula



wherein

G is

(1) NH_2 or

(2) substituted amino;

R_9 is

(1) hydrogen,

(2) loweralkyl,

(3) carboxy-substituted alkyl or

(4) carboxyester-substituted alkyl;

R_{10} is

(1) hydrogen,

(2) loweralkyl,

(3) functionalized alkyl or

(4) cycloalkyl;

D is

(1) hydrogen,

(2) loweralkyl,

(3) functionalized alkyl,

(4) cycloalkyl,

(5) aryl,

(6) functionalized oxyalkyl or

(7) heterocyclic;

with the proviso that D is other than indolylmethyl, indolinylmethyl or oxindolylmethyl;

or R_{10} taken together with D is

(1) C_4 to C_6 alkylene,

(2) $-(CH_2)_q-V-(CH_2)_r-$ wherein q is 1 to 3, r is 1 to 3 and

V is

(i) -O-,

(ii) -S-,

(iii) $-CH_2-$ or

(iv) $-N(R_{25})-$ wherein R_{25} is hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, arylalkyl, aryl or an N-protecting group;

or R_9 taken together with D is

(1) C_3 to C_5 alkylene or

(2) $-(CH_2)_p-V-(CH_2)_t-$ wherein p is 1 to 3, t is 1 to 3 and V is defined as above;

Z is

(1) -C(O)-,

(2) -C(S)- or

(3) $-S(O)_2-$;

B is

(1) absent,

(2) alkylene,

(3) alkenylene,

(4) substituted alkenylene,

(5) $-R_{26}-R_{27}-$ wherein R_{26} is absent or $-CH_2-$ and R_{27} is -O-, -S-, -NH- or -N(loweralkyl)- or

(6) $-R_{27}-CH_2-$ wherein R_{27} is defined as above; and

Ar is

(1) aryl or

(2) a heterocyclic group.

2. The compound of Claim 1 wherein D is

(1) aryl,

(2) arylalkyl,

(3) heterocyclic,

(4) heterocyclicalkyl,

(5) functionalized oxyalkyl,

(6) loweralkyl substituted by $-NHC(O)R_4$ wherein R_4 is loweralkyl, alkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or

(7) loweralkyl substituted by -S-loweralkyl, -S(O)-loweralkyl, $-S(O)_2$-loweralkyl, -S-aryl, -S(O)-aryl or $-S(O)_2$-aryl; and

Ar is heterocyclic.

3. The compound of Claim 1 wherein Ar is heterocyclic; B is absent; Z is -C(O)-; R_9 and R_{10} are hydrogen; D is loweralkyl, functionalized oxyalkyl, aryl or heterocyclic; and G is substituted amino.

4. The compound of Claim 3 wherein Ar is quinolyl, hydroxyquinolyl or dihydroxyquinolyl; D is phenyl,

heterocyclic, hydroxyalkyl or alkoxyalkyl; and G is dialkylamino.

5. A compound selected from the group consisting of:
N-(3'-Quinolylcarbonyl)-(2R,3S)-(O-methyl)Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-(2R,3S)-Threonine-di-n-pentylamide;
N-(3'-Quinolylcarbonyl)-R-Histidine-di-n-pentylamide dihydrochloride;
N-(3'-Quinolylcarbonyl)-R-Phenylglycine-di-n-pentylamide; and
N-(4',8'-Dihydroxy-2'quinolylcarbonyl)-R-Phenylglycine-di-n-pentylamide.

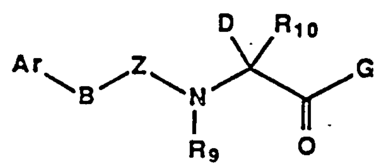
6. A method for antagonizing CCK comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

7. A method for treatment or prevention of hyperinsulinemia or disorders of the gastrointestinal, central nervous, appetite regulating or pain regulating systems comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

8. A pharmaceutical composition for antagonizing CCK comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 1.

9. A pharmaceutical composition for treatment or prevention of hyperinsulinemia or disorders of the gastrointestinal, central nervous, appetite regulating or pain regulating systems comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 1.

10. A process for the preparation of a compound of the formula:



wherein

G is

(1) NH_2 or

(2) substituted amino;

R_9 is

(1) hydrogen,

(2) loweralkyl,

(3) carboxy-substituted alkyl or

(4) carboxyester-substituted alkyl;

R_{10} is

(1) hydrogen,

(2) loweralkyl,

(3) functionalized alkyl or

(4) cycloalkyl;

D is

(1) hydrogen,

(2) loweralkyl,
(3) functionalized alkyl,
(4) cycloalkyl,
(5) aryl,
(6) functionalized oxyalkyl or
(7) heterocyclic;

with the proviso that D is other than indolylmethyl, indolinylmethyl or oxindolylmethyl;

or R_{10} taken together with D is

(1) C_4 to C_6 alkylene,
(2) $-(CH_2)_q-V-(CH_2)_r-$ wherein q is 1 to 3, r is 1 to 3 and
V is
(i) -O-,
(ii) -S-,
(iii) $-CH_2-$ or
(iv) $-N(R_{25})-$ wherein R_{25} is hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, arylalkyl, aryl or an N-protecting group;

or R_9 taken together with D is

(1) C_3 to C_5 alkylene or
(2) $-(CH_2)_p-V-(CH_2)_t-$ wherein p is 1 to 3, t is 1 to 3 and V is defined as above;

Z is

(1) -C(O)-,
(2) -C(S)- or
(3) $-S(O)_2-$;

B is

(1) absent,

(2) alkylene,

(3) alkenylene,

(4) substituted alkenylene,

(5) $-R_{26}-R_{27}-$ wherein R_{26} is absent or $-CH_2-$ and R_{27} is -O-, -S-, -NH- or -N(loweralkyl)- or

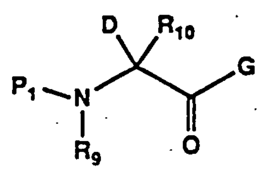
(6) $-R_{27}-CH_2-$ wherein R_{27} is defined as above; and

Ar is

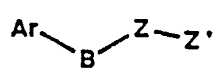
(1) aryl or

(2) a heterocyclic group;

comprising coupling an amine of the formula



wherein P_1 is hydrogen with a compound of the formula



wherein Z' is an activating group; or B-Z-Z' taken together represent -N=C=O, -N=C=S, $-CH_2-N=C=O$ or $-CH_2-N=C=S$.